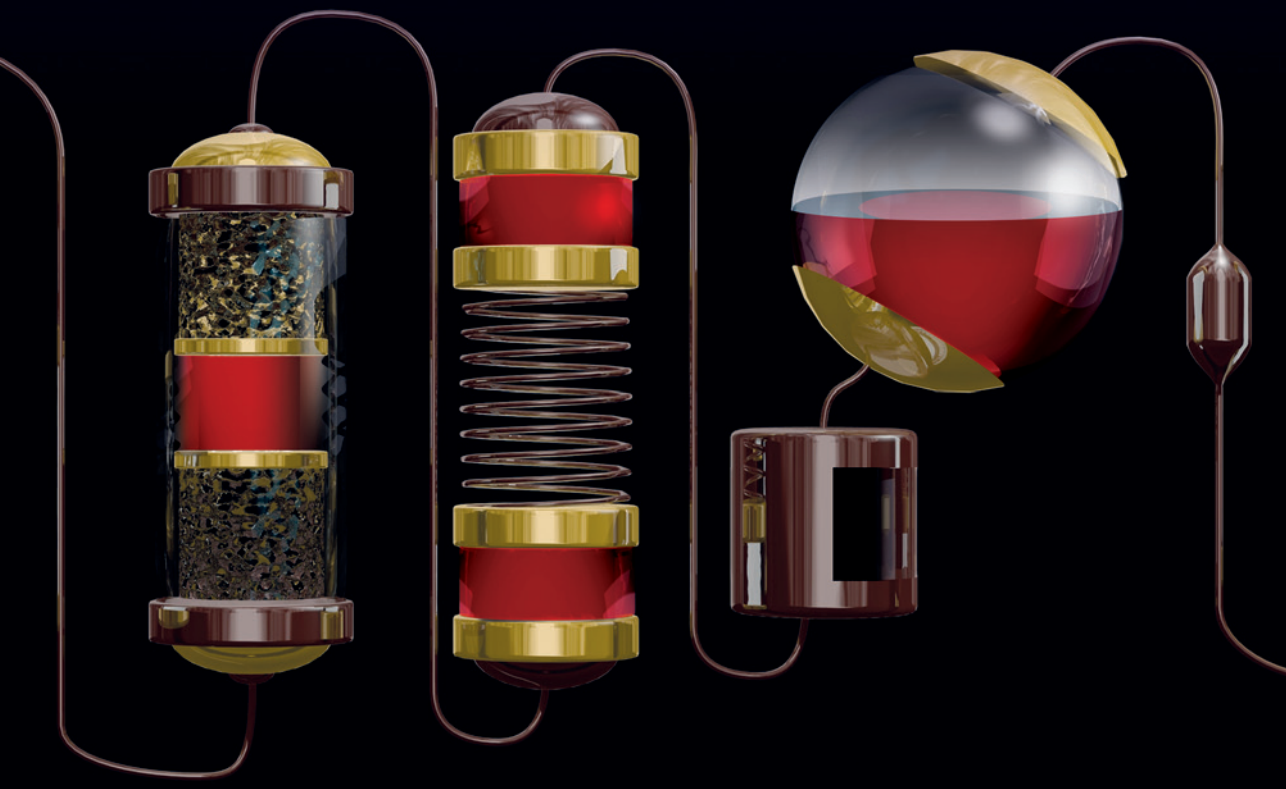
Cardiovascular and cerebrovascular physiological measurements in clinical practice and prognostics in geriatric patients



Joep Lagro

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Cardiovascular and cerebrovascular physiological measurements in clinical practice and prognostics in geriatric patients

Proefschrift

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Chapter 1

Introduction

General introduction

Case description

Mrs. X. is a 88 year old women who has been referred to our falls and syncope outpatient department because of a recent fall, probably with syncope, and a history of recurrent falls. Mrs. X. has a medical history of Alzheimer's dementia (AD), obesity, hypertension, osteoporosis, osteo-arthritis and myocardial infarction for which she uses eight different medications, including a cholinesterase inhibitor for AD. She quitted smoking after her myocardial infarction approximately 10 years ago and consumed alcohol sporadically. Mrs. X. has worked as a kindergarten teacher, before she got married with her husband and has three children. After the children left the house she worked as a secretary in a great company. Her children live at a large distance, but the relation with them is good. She and her 91 year old husband live independently with a little help from their neighbors and children.

Because of her AD she cannot tell exactly what happened when she lastly fell. Her 91 year old husband found her three times lying on the ground calling for help in the past six months. He witnessed only one fall. He described that she lost her consciousness after standing up from the dining table, where they had enjoyed diner half an hour earlier, and walked to the kitchen to put a carafe above the sink. After she fell, she regained consciousness very quickly in less than a minute. Luckily she did not hurt herself and recognized her husband immediately. Her husband did not notice any particularities during syncope. Afterwards there were no specific complaints.

Besides a standard comprehensive geriatric assessment, she underwent a SMC-test (Stand, Meal and Carotid sinus massage) protocol in the morning, after an overnight fast, including abstaining from her morning medication. This test is meant to detect orthostatic hypotension (OH), postprandial hypotension (PPH) and carotid sinus hypersensitivity (CSH), respectively. During the SMC-test the blood pressure (BP) was measured continuously, non-invasively with the Finometer (Finapres Medical Systems, Amsterdam, the Netherlands). Heart rate was recorded with a double lead ECG. Upon standing (Stand test) her BP dropped from a baseline BP of 170/85 mmHg after 10 minutes of supine rest to a minimum of 130/60 mmHg in the first 15 seconds. She was asymptomatic and BP recovered very quickly to 180/85 mmHg after 1 minute of standing. Hereafter a minimum of BP of 140/60 mmHg was reached after approximately 2 minutes of standing. At this time, she complained of transient fatigue and light-headedness. She could not recollect if she experienced the same complaints when she fell at home. After eating a standardized meal (Meal-test), BP dropped from the baseline BP of 170/85 mmHg to a minimum of 145/75 mmHg after 30

minutes without experiencing complaints. Lastly, carotid sinus massage was performed in the supine position. On the right side, BP decreased from the baseline BP of 170/85 mmHg to 125/65 with a maximum R-R interval of 2.2 seconds. On the lift side, BP decreased to 130/60 with a maximum R-R interval of 3.1 seconds. During both carotid sinus massages, she remained asymptomatic.

In summary, these observations during blood pressure stress tests showed that Mrs. X. had symptomatic OH, asymptomatic PPH and asymptomatic CSH, without showing evidence for syncope (for criteria of OH, PPH, and CSH, see below). Mrs. X. illustrates a typical, average patient seen on our falls and syncope outpatient clinic and her case illustrates the complex nature of falls and syncope in the elderly. This case raises several questions which form the basis of this thesis.

First, in Mrs. X. three geriatric hypotensive syndromes (OH, PPH, and CSH) occur together. Is this by chance, because these three hypotensive syndromes are common in old age, or do these three syndromes share a common pathophysiology? Second, do these syndromes predict mortality? Is the occurrence of these hypotensive syndromes in Mrs. X. an indicator for a shorter life expectancy? Third, in line with the second question, does a large BP decrease immediately after standing, but also the amount of recovery afterwards, predict mortality? Fourth, is Mrs. X. prone to these BP regulation disorders, because of her neurodegenerative AD, which might affect central BP regulation mechanisms? Have patients with AD worse BP regulation? Does her cholinesterase inhibitor use influences BP regulation? Finally, it is very relevant in case of Mrs. X. to know whether she is at high risk for more symptoms of hypoperfusion of the brain due to her AD, because of a possibly affected cerebral autoregulation with AD? As such, the final question is whether AD-patients on average have impaired cerebral autoregulation?

Background

Before discussing these research questions in more detail, some background information on BP regulation and cerebral autoregulation is provided below. Cerebral blood flow is maintained stable through combined effects of BP regulation and cerebral autoregulation.(1-3)

Blood pressure regulation

Arterial BP is determined by cardiac output and peripheral resistance. Cardiac output is the result of heart rate and stroke volume. Stroke volume is related to myocardial contractility and the size of the vascular compartment (intravascular blood volume, Frank-Starling law).(4) Peripheral resistance is determined by

the structure and function of small arteries and arterioles.(5,6) Although the regulation of arterial BP is not fully understood, the following mechanisms play a role in BP regulation.(4,6-8)

1) Neural regulation by the autonomic nervous system

The central autonomic nervous system receives BP information from baroreceptors (and other receptors, like chemoreceptors), and controls BP to keep fluctuations small through the baroreflex.(4,6) The baroreflex is a reflex loop with cardiac, vascular, and cerebral components involved in short-term BP regulation.(9,10) The arterial baroreflex is induced by nerve receptors called baroreceptors, which are located mainly in the walls of the aorta in the chest and the walls of the internal carotid arteries in the neck.(8) These receptors are stimulated when increased pressure stretches the vessel walls.(10) The receptors send signals to the cardiovascular control center in the medulla oblongata.(6,10) From here afferent nerves run to atria, ventricles, arteries, arterioles, venules, veins and adrenal glands.(6) The baroreflex operates via the autonomic nervous system to restore sudden changes in BP by changing heart rate or vascular tone. A clinical example is the drop in BP upon standing, which the baroreflex corrects by a rapid increase in heart rate (parasympathetic inhibition) followed by peripheral arterial vasoconstriction and increased cardiac contractility (sympathetic activation).(10) The parasympathethic system operates faster than the sympathetic system. Heart rate changes mediated by signals though the vagal nerve have a latency of about 0.5 seconds and a time constant of a few seconds, whereas these values are 1-3 seconds and 10 seconds respectively for the sympathicus.(11) This baroreflex is impaired with advancing age(1,9,10,12,13) and increasing BP levels. (9,10,12). Endurance training improves cardiac baroreflex function.(1,14). Remarkably, there still is a paucity of data on the baroreflex function in patients with AD and on the effects of drug application in AD.(15) The main neurotransmitter for the parasympathetic autonomic system is acetylcholine. Theoretically, the use of an acethylcholinesterase inhibitor might improve baroreflex function. Prospective data collection on these issues is still required, for safe and evidence based prescription of acetylcholinesterase inhibitors.

2) Humoral regulation

The best known hormonal system to regulate BP is the Renin-Angiotensin-Aldosterone-System (RAAS).(4) The RAAS is activated when low BP causes the blood flow through the kidneys to fall below normal. The low flow makes the kidneys secrete renin into the blood and splits angiotensin I from angiotensinogen. Angiotensin I is converted to Angiotensin II by angiotensin-converting enzyme. Angiotensin II is the dominant effector molecule of the RAAS and constricts the

small arteries throughout the body and promotes renal tubular sodium and water retention, by secretion of aldosterone by the adrenal cortex.(7,8) The renin-angiotensin vasoconstrictor mechanism operates in minutes.(8) Aldosterone has its BP regulating effects in hours. Besides the RAAS, other classical circulating hormones, like catecholamines and vasopressin also play a role in BP regulation.

3) Renal volume regulation

The kidneys importantly contribute to BP regulation by their key role in regulating body fluid volume through their water conservation and the opposing diuretic function.(4,6) When the arterial pressure rises above normal, the excess pressure causes the kidneys to excrete more water and salt than are entering the body. Therefore, the blood volume decreases. This causes the heart to pump less blood, and the arterial pressure to fall.(8) This kidney-fluid system is a slow acting regulator which exert its influence in days.(8)

The different mechanisms are not working in isolation, there is considerable neuro-humoral interaction present.(4) For example, the kidneys are innervated by the sympathetic autonomic nervous system and vasopressin reduces the baroreceptor sensitivity.(4)

Variability of heart rate and blood pressure

BP and heart rate continuously fluctuate over time, under the influence of the above mentioned control mechanisms, which together safeguard cardiovascular homeostasis.(16) Therefore, this variability directly reflects the activity of cardiovascular control mechanisms.(16) Consequently, heart rate variability (HRV) and blood pressure variability (BPV) are used to explore autonomic cardiovascular modulation. However, while HRV largely reflects selective autonomic control of the heart, BPV is the result of complex interactions between multiple mechanisms.(17) Nevertheless HRV or BPV can provide a valuable insight into integrated cardiovascular regulation.(17) The advantages of this approach are that it is easy applicability in daily practice and that it avoids any external intervention on subjects under evaluation.(16,17) HRV and BPV, but also the earlier mentioned baroreceptor sensitivity are established and frequently used measures of cardiovascular autonomic function in research.(10,18,19) In these thesis we will use several non-invasive indices of HRV, BPV and baroreceptor sensitivity to determine autonomic function and to study its role in hypotensive syndromes (see below). Although autonomic dysfunction plays a important role in specific diseases, such as multiple system atrophy, Parkinson's disease, pure autonomic failure and diabetic and amyloid neuropathy(19,20), its role in geriatric hypotensive syndromes is less clear.

Hypotensive syndromes

OH, PPH and CSH are disorders of BP regulation with high prevalence in the elderly.(21-23) If the cerebral circulation becomes critically compromised by these hypotensive syndromes, susceptible individuals may experience weakness, fatigue, blurred vision, dizziness, pain in the neck and shoulders ('coat hanger' pain) and syncope.(3,24,25) Therefore, detection and management of these hypotensive syndromes is crucial in order to improve quality of life of patients, prevent syncopal attacks and fall-related injuries, and to optimize treatment of concomitant diseases, such as hypertension and heart failure.(20,24)

OH is the best known hypotensive syndrome. OH is defined as a systolic blood pressure (SBP) decrease of 20 mmHg or more or to below 90 mmHg and/or a diastolic blood pressure (DBP) decline of 10 mmHg or more between 1 and 3 minutes after standing from supine.(24) Recently a new consensus on orthostatic intolerance syndromes has been reached(25), with a decrease in SBP of 30 mmHg of more suggested to be a more appropriate diagnostic limit among hypertensive patients (i.e. those with supine SBP of 160 mmHg or more). Besides "classical" OH, also an initial BP decrease directly after standing with subsequent recovery in the first minute can be distinguished.(26) This initial response can only be measured with continuous noninvasive monitoring.(25) The (patho-) physiology of BP decline directly after standing is as follows. Moving from the supine to upright posture results in the translocation of 300-1000 mL of blood from the central intravascular compartment to dependent regions in the legs, buttocks, pelvis and splanchnic circulation.(19,20,25) As a result, the venous return to the right atrium and the thoracic blood and stroke volume are all reduced, and reflex chronotropic and vasoconstrictive responses mediated by increased sympathetic outflow and decreased vagal activity compensate to maintain arterial pressure in the upper body at the pre-orthostatic level, respectively.(20,25-27) If, one continues to stand, transcapillary filtration in the subdiaphragmatic space additionally reduces the central blood volume with about 15%(3,6,20,27), while the cardiac output decreases by nearly 20%.(20,27) In a healthy subject, however, mean arterial pressure is preserved, because of compensatory increases in vascular tone in splanchnic, musculocutaneous and renal areas.(3,20) The rapid circulatory adjustments are governed merely by autonomic neural pathways, whereas circulatory changes that occur during the prolonged orthostatic challenge involve neurohumoral mechanisms, such as activation of the renin-angiotensin system(3,20).

PPH is defined as a SBP decline of 20 mmHg or more within 75 minutes after a meal.(28,29) PPH appears to result from inadequate compensation for the normal physiologic postmeal decrease in BP, rather than from an exaggerated amount of splanchnic pooling.(30) A blunted sympathetic response to hypotension appears

to be responsible for the compensatory failure that underlies PPH. A micro-neurographic study of muscle sympathetic activity demonstrated that elders respond to an oral glucose load with a smaller increase in sympathetic activity, in comparison with younger subjects.(30,31) Stretch receptors in the stomach normally also can activate sympathetic signaling, by which gastric distention normally has a pressor effect. However, in the elderly, this "gastrovascular reflex" is blunted.(30,32) This statement is also supported by the observation that there is no difference in muscle sympathetic nerve activity between the healthy elderly and young patients in response to an *intraduodenal* glucose load.(30,33)

CSH is defined as an interruption of heart rate over at least 3 seconds and/or as a decrease of SBP of 50 mmHg or more after carotid sinus massage.(24) The pathophysiological processes underlying CSH remain poorly understood.(34) Perhaps CSH is associated with neurodegeneration and may be part of more widespread autonomic dysfunction, rather than a localized disorder within the carotid sinus.(34,35)

In elderly patients 85 years of age or older, the association between BP and mortality or cardiovascular risk is absent or less strong than in younger patients.(5,36) OH predicts mortality in middle-aged patients(37-39), however the association in elderly patients seems inconsistent.(40-43) The information on PPH or CSH and mortality is sparse.(28,29,44,45)

Cerebral autoregulation

Cerebral blood vessels have an inherent ability to keep cerebral blood flow constant in response to changes in arterial BP or intracranial pressure.(2) In response to a variation in perfusion pressure (mean arterial pressure – intracranial pressure), an adaptation in cerebrovascular resistance by means of myogenic, neurogenic or metabolic mechanisms will cause cerebral blood flow to return to its baseline.(2,46-48) This hemodynamic process is known as cerebral autoregulation.(2,46,47,49) The term autoregulation within the cerebral circulation was introduced by Lassen in 1959.(2,46) Lassen introduced the classic cerebral autoregulatory curve in which cerebral blood flow remains constant over a wide range of BP, the plateau phase, with the upper and lower limits forming the boundaries of cerebral autoregulation.(2,46,47) This curve reflects static cerebral autoregulation and is composed of several different studies that assess the semi-steady state reactions of cerebral blood flow on sustained periods of hypertension or hypotension by pharmacological interventions. However, the clinical applicability of this artificially created static cerebral autoregulation estimation is limited.(2) Technological developments as transcranial Doppler ultrasonography(49,50) and servo-controlled finger photoplethysmography(51) (Finapres) have offered possibilities to investigate the dynamics of cerebral

autoregulation. In contrast to studies of the static cerebral autoregulation, dynamic studies of cerebral autoregulation quantify the fast modifications in cerebral blood flow velocity in a major cerebral artery in relation to rapid alterations in BP within the upper and lower limits of static cerebral autoregulation.(2) For studies of dynamic cerebral autoregulation, a pharmacological intervention is not required, and the method is entirely noninvasive, which makes it clinically suitable in frail older patients, even when they suffer from AD. However, these dynamic studies are not able to measure flow at the brain tissue level.(2) Additionally, noninvasive information of change of blood volume level in the brain tissue can be obtained with near infrared spectroscopy (NIRS).(52) The impact of AD on dynamic cerebral autoregulation is not well know, but is important to be studied to understand the variability in the presentation of symptoms in patients with geriatric orthostatic syndromes.(53)

Aims

Given the impact and high prevalence of hypotensive syndromes and AD, the relevance of the questions raised from daily clinical practice, and on the basis of lack of knowledge on these issues as described above, this thesis addresses three different but coherent questions related to BP and cerebral autoregulation.

First, we investigate evidence for a direct role of autonomic dysfunction in the etiology of geriatric hypotensive syndromes in falls patients, and whether these hypotensive syndromes share a common pathophysiology. With abundant evidence on the important role of autonomic dysfunction in syncope in younger patients, the role of autonomic dysfunction of geriatric hypotensive syndromes is unclear.

Second, we investigate the correlation of these hypotensive syndromes with mortality. Besides the relation of the different hypotensive syndromes with mortality, we also looked at the relationship with mortality of the amount of BP decline, and the ability of BP recovery. As pointed out above, the research on the association of OH, PPH and CSH and mortality in elderly patients is inconsistent or sparse.

Third, we examined the role of AD on BP regulation, through baroreflex functioning and the impact of AD on dynamic cerebral autoregulation. AD and cardiovascular disease share the same risk factors.(54) Vascular factors may partially cause or aggravate AD(54), but AD may also directly cause alterations of BP regulation and dynamic cerebral autoregulation by the neurodegenerative process in relevant brain centres and strongly related cerebral amyloid angiopathy. Hence, it's also highly relevant to investigate the influence of AD on these regulatory mechanisms.

Outline of this thesis

Chapter 2a investigates the association between three hypotensive syndromes (OH, PPH and CSH) and several non-invasive autonomic function measures in a cross-sectional study of geriatric patients visiting our outpatient falls clinic. **Chapter 2b** is a letter to the editor in which some remarks are made by us about the relevance and shortcomings of a proposed monocausal diagnostic syncope test for a heterogenic geriatric falls population with multicausal etiology.

Chapter 3a researches the possibly shared pathophysiology of three hypotensive syndromes (OH, PPH and CSH). Also the impact on mortality of these three syndromes is studied in a retrospective cohort study design of elderly patients visiting our outpatient falls clinic. Finally, the relation between the amount of BP decline during testing for the above mentioned hypotensive syndromes and mortality is investigated. **Chapter 3b** is a letter to the editor highlighting the rationale and relevance to perform our study. **Chapter 3c** is a letter to the editor questioning the role of DBP decline during OH in middle aged adults.

Chapter 4 studies the association between the amount of BP decline directly after active standing and mortality in a retrospective design. The association with mortality was also investigated for the BP recovery after the initial BP decline.

Chapter 5a investigates the baroreflex functioning in patients with AD, patients with mild cognitive impairment and healthy elderly. Also the influence of cholinesterase inhibitors on baroreceptor sensitivity is studied. **Chapter 5b** is a letter to the editor which discusses the potential additive role of BPV, above absolute BP, on cognitive decline in older people. This as an example of the complex reciprocal interaction of vascular factors and cognition.

Chapter 6 assesses the dynamic cerebral autoregulation in patients with AD and healthy elderly with transcranial Doppler and NIRS.

In **Chapter 7** the preceding chapters are summarized and discussed in the light of previous research, and future perspectives.

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Chapter 2a

Geriatric hypotensive syndromes are not explained by cardiovascular autonomic dysfunction alone

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Abstract

Background

Though highly prevalent, the pathophysiology of orthostatic hypotension (OH), postprandial hypotension (PPH), and carotid sinus hypersensitivity (CSH) are rarely studied together. Therefore we conducted such a comprehensive study focusing on the common role of the cardiovascular autonomic system. We hypothesized that in geriatric patients, OH, PPH and CSH are manifestations of cardiovascular autonomic dysfunction, and investigated state-of-the-art cardiovascular autonomic function indices in a group of geriatric falls or syncope patients.

Methods

In a cross-sectional study of 203 consecutive eligible falls clinic patients, we compared heart rate variability (HRV), blood pressure variability (BPV), and baroreflex sensitivity (BRS) as potential autonomic function determinants of the three different hypotensive syndromes.

Results

OH, PPH, and CSH were diagnosed in 53%, 57%, and 50% of the patients, respectively. In a population relevant for geriatric practice, we found no differences in HRV, BPV, and BRS between patients with and without OH, with and without PPH and with and without CSH, respectively, nor between patients with and without falls, dizziness or syncope as presenting symptom, respectively.

Conclusions

In geriatric patients with hypotensive syndromes, cardiovascular autonomic function as measured by HRV, BPV, and BRS is comparable to patients without such syndromes. These findings argue against a single or dominant etiological factor, that is, cardiac autonomic dysfunction and underline the structured, broad and multifactorial approach to elderly patients with falls and/or syncope as proposed in the current evidence-based syncope guidelines.

Introduction

Heart rate variability (HRV), blood pressure variability (BPV), and baroreceptor sensitivity (BRS) are established measures of cardiovascular autonomic function in research.(1-3) The clinical relevance of these measures has also been shown, as diminished BRS, diminished HRV, and increased BPV have prognostic significance for mortality and cardiovascular risk.(4-6)

Orthostatic hypotension (OH), postprandial hypotension (PPH), and carotid sinus hypersensitivity (CSH) are disorders of blood pressure (BP) regulation with high prevalence in the elderly patients.(7-12) OH is predominantly seen as a disorder of autonomic failure, and PPH and CSH are classified as reflex or neurally mediated syncope.(13) The cardiovascular autonomic system plays an important role in the distribution of blood volume and the regulation of BP,(8;14-17) and failure of this system might play an important role in the etiology and pathophysiology of these hypotensive syndromes.

Therefore, we hypothesized that commonly available and non-invasive autonomic function indices of HRV, BPV and BRS are different in patients with and without OH, PPH, and CSH.

Methods

Study Population

This study included 242 consecutive patients, who visited the geriatric outpatient falls and syncope clinic of the Radboud University Nijmegen Medical Centre because of falls, dizziness and/or syncope. This test protocol was part of the standard diagnostic work-up. Patients were excluded if they were unable to follow the instructions due to delirium, psychosis or very severe dementia (Clinical Dementia Rating 3), if they were unable to stand for 10 min or drink a test meal of 200 mL within 10 min. Furthermore patients were excluded for CSH testing in case of a recent (less than 3 months) myocardial infarction, transient ischemic attack or stroke respectively, a medical history of ventricular tachyarrhythmias or the presence of a carotid bruit.(18)

The protocol conformed to the Declaration of Helsinki and informed consent was asked verbally prior to the tests.

Baseline Assessment

Preceding OH, PPH and CSH testing, patients underwent a complete medical history and physical examination. Baseline characteristics (age, gender, body mass index (BMI), systolic BP (SBP), diastolic BP (DBP) and heart rate (HR)) were measured. The presence and severity of comorbidity was recorded using the

Cumulative Illness Rating Scale for Geriatrics (CIRS-G), ranging from 0 to 56.(19) For medical history we used the following disease groups: dementia; depression or anxiety disorder; chronic obstructive pulmonary disease; diabetes mellitus; Parkinson's disease or disorders with parkinsonism; cardiovascular disease (CVD) including myocardial infarction, angina pectoris, heart failure, peripheral vascular disease, aneurysm of the aorta, stroke, and transient ischemic attack; hypertension; and malignancy.

Test Protocol

Patients fasted overnight and medication was withheld from midnight the night before. All tests were performed in the morning or afternoon. During the tests BP and HR were constantly measured using a beat-to-beat finometer (Finapres™) (20) and a three-lead electrocardiogram (ECG). BP was measured at the non-dominant arm, which was held at heart level with a sling.

The test protocol started with the OH test, followed by the PPH test and finished with the carotid sinus massage (CSM). Before testing and at each time-point during tests (OH test every minute, PPH test every 5 min), BP and HR were determined. The reported BP values are averages of 20 heartbeats (10 before and 10 after each time-point). For CSH testing, BP values were determined by taking the average of 3 heartbeats around the lowest BP value during or in a 30-s period after CSM. From the ECG registration, the R-R interval before and the longest interval during or in a 30-s period after CSM were documented. At each time-point symptoms of possible cerebral hypoperfusion, like dizziness, light-headedness, fatigue or loss of consciousness were noted.

Orthostatic hypotension test

After a 10 min resting period in the supine position, patients were asked to stand up and remain standing for 10 min. Baseline values of BP and HR were defined as the average during the 60 s before rising. OH was defined as a SBP decline of 20 mmHg or more or a DBP decline of 10 mmHg or more within 3 min of standing from supine.(13)

Postprandial hypotension test

The patient was asked to drink a test meal within 10 minutes in sitting position. The test meal is a solution of 100 mL glucose syrup and 100 mL lactose free milk, containing 292 kcal, 65 g carbohydrates, 2 g fat and 4 g protein. The meal temperature was 20-25 °C.(21) After drinking the meal, BP and HR were monitored during 75 min. PPH was defined as a SBP decline of 20 mmHg or more within 75 min after a meal.(7;9)

Carotid sinus massage

CSM was performed in supine position after 5 min rest. Firm, longitudinal massage was performed for 5 s over the site of maximal pulsation of the right carotid artery and repeated on the left side when SBP and HR were normalized. If no significant response in SBP or HR was obtained with supine CSM, the procedure was repeated with the patient tilted at 70° on a tilt-table with footplate. CSH is defined as an interruption of heart beat more than at least 3 s or as a decrease of SBP of 50 mmHg or more.

Assessment of HRV, BPV, and BRS

Data were analyzed with custom-written software in Matlab (version R2010b, the MathWorks Inc., Natick, Massachusetts). The 10 min resting period in supine position was used to select an appropriate period to determine the measures of HRV, BPV, and BRS. Not necessarily the same periods were used to calculate HRV, BPV, or BRS.

Heart rate variability

The standard deviation of all normal beat intervals (SDNN-HRV) and the square root of the mean squared difference of successive beat intervals (RMSSD-HRV) were used for conventional time domain measurements.(1) The data were linearly detrended and filtered with a third-order Butterworth filter with a cut-off frequency of 0.03 Hz and resampled to 4 Hz using linear interpolation. Artifact-free data series of 100 s were used. With spectral analysis the power of HRV was calculated in the low (LF-HRV; 0.04-0.15Hz) and high (HF-HRV; 0.15-0.4Hz) frequency band as conventional frequency domain measurements. (1) Also the ratio of LF-HRV and HF-HRV was determined (LF/HF-HRV).

Blood pressure variability

The BPV was also analyzed in the time and frequency domain. Only the systolic BP was used. The standard deviation of BP (SD-SBP) and the square root of the mean squared difference of successive BP beats (RMSSD-SBP) were used for conventional time domain measurements. The data were linearly detrended and filtered with a third-order Butterworth filter with a cut-off frequency of 0.05 Hz and resampled to 1 Hz using linear interpolation. Only uninterrupted data series of at least 50 s were used for the spectral analysis. With spectral analysis the power of BPV was calculated in the low (LF-SBP;0.05-0.15Hz) and high (HF-SBP;0.15-0.4Hz) frequency band. These frequency bands were defined largely in line with the standards of the European Society of Cardiology for HRV, meaning LF=0.04-0.15 Hz and HF=0.15-0.4 Hz.(1) However, because a filter with cut-off frequency 0.05 Hz was used as recommended by Bernardi et al.(22), LF for BPV was chosen between 0.05 and 0.15 Hz.

Baroreflex sensitivity

BRS was quantified in the time domain with the sequence and the standard deviation method (SD-BRS) and in the frequency domain with spectral analysis. The sequence method was applied for positive (SQ-BRS+) and negative (SQ-BRS-) sequences.(23) The SD-BRS method calculates the BRS by dividing the standard deviation of the heartbeat interval by the standard deviation of SBP (SD-BRS). The SD-BRS is an easy, robust and reliable method to calculate BRS.(22)

The data were linearly detrended and filtered with a third-order Butterworth filter with a cut-off frequency of 0.05 Hz and resampled to 1 Hz using linear interpolation. Data series of at least 50 s were used. In the frequency domain BRS is calculated in the low (0.05-0.15 Hz) and high (0.15-0.4 Hz) frequency band by dividing the spectral power of the heartbeat interval through the spectral power of SBP, only if the coherence more than 0.5.(24) Heartbeat intervals were derived from the BP peaks to overcome artifacts in the ECG.(25)

Statistical Analysis

We compared the patients with and without OH, PPH and CSH, respectively. We used only those patients who completed all three tests. Because there is frequent co-existence of multiple hypotensive syndromes in the same patient we also compared patients with no single hypotensive syndrome versus one, two, or three hypotensive syndromes. We also compared patients with and without falls, dizziness or syncope as presenting symptom. Finally, we made a comparison between patients who presented with falls and patients who presented with syncope.

Baseline characteristics of the patients were compared with independent sample Student's t-tests or one way analysis of variance and chi-square (χ^2) statistics. Results are presented as mean ± standard deviation (SD) or percentages.

Normality of HRV, BPV, and BRS measures was tested with the Kolmogorov-Smirnov test. If the data were not normal distributed they were logarithmically transformed and tested again for normality. None of the HRV, BPV, and BRS measures had a normal distribution. After logarithmic transformation all data were normal distributed except for the SQ-BRS+, SQ-BRS- and SD-SBP data. Means were compared with independent sample Student's t-tests or one way analysis of variance for normal distributed data, otherwise Mann-Whitney's U tests or Kruskal-Wallis tests were used. Because we compared 14 different measures of cardiovascular autonomic function, we choose an alpha of 0.01, instead of 0.05 to correct for multiple testing. Results for HRV, BPV, and BRS measures are presented as medians with the 25th - 75th percentile range. All analyses were performed using the SPSS software version 16 for windows (SPSS Inc., Chicago, Illinois).

Results

Baseline Characteristics

Of the 242 patients, 203 (84%) patients completed all three tests. CSM was not performed in 34 patients because they met the exclusion criteria. Of five patients there was no value for OH and/or PPH tests due to unreliable measurements (no good signal). Of these 203 patients, 53%, 57%, and 50% were diagnosed with OH, PPH and CSH and 87% patients were diagnosed with at least one or more hypotensive syndromes.

Baseline characteristics of patients with and without different hypotensive syndromes were compared (Table 1). Compared with the patients without OH, the patients diagnosed with OH had lower BMIs and had higher mean baseline SBP ($p<0.05$). The patients with PPH were older, had higher baseline SBPs and had more frequently a medical history of CVD ($p<0.05$). The patients with CSH had lower BMIs, presented less often with dizziness and used less angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists compared with those without CSH ($p<0.05$). There were no differences in comorbidity (CIRS-G) nor the number of drugs used.

Table 1 Comparison of the Baseline Demographic and Clinical Characteristics of the Patients With and Without Orthostatic Hypotension, Postprandial Hypotension and Carotid Sinus Hypersensitivity

Variable	OH– (n=95)	OH+ (n=108)	PPH– (n=87)	PPH+ (n=116)	CSH– (n=102)	CSH+ (n=101)
Age	76.9±8.6	78.4±7.4	75.6±8.0	79.3±7.6†	76.7±9.0	78.7±6.7
BMI	27.3±4.9	26.0±4.2*	27.3±4.7	26.1±4.4	27.2±4.8	26.0±4.2‡
Female, n(%)	55(58%)	74(69%)	59(68%)	70(60%)	63(62%)	66(65%)
Baseline SBP	162±24	171±25*	160±22	172±26†	164±25	169±25
Baseline DBP	78±11	80±13	79±12	79±12	79±12	79±12
Baseline HR	67±11	68±12	68±12	67±11	68±12	68±11
CIRS-G total score	10.6±4.6	11.3±4.4	10.5±4.3	11.3±4.6	10.9±4.4	10.9±4.5
Presenting symptom						
Falls	79(83%)	96(90%)	74(86%)	101(87%)	90(89%)	85(84%)
Dizziness	48(51%)	55(51%)	41(48%)	62(53%)	61(60%)	42(42%)‡
Syncope	29(31%)	37(35%)	28(33%)	38(33%)	36(36%)	30(30%)
Symptomatic	-	67(62%)	-	46(40%)	-	51(51%)

Table 1 Continued

Variable	OH– (n=95)	OH+ (n=108)	PPH– (n=87)	PPH+ (n=116)	CSH– (n=102)	CSH+ (n=101)
Medical history						
Dementia	6(6%)	6(6%)	4(5%)	8(7%)	4(4%)	8(8%)
Depression or anxiety	15(16%)	21(19%)	20(23%)	16(14%)	19(19%)	17(17%)
COPD	16(17%)	19(18%)	15(17%)	20(17%)	16(16%)	19(19%)
Diabetes mellitus	13(14%)	16(15%)	9(10%)	20(17%)	18(18%)	11(11%)
Parkinson(ism)	4(4%)	6(6%)	3(3%)	7(6%)	7(7%)	3(3%)
CVD	31(33%)	42(39%)	20(23%)	53(46%)†	37(36%)	36(36%)
Hypertension	42(44%)	50(46%)	37(43%)	56(48%)	53(52%)	40(40%)
Malignancy	15(16%)	25(23%)	14(16%)	26(22%)	19(19%)	21(21%)
Medication use						
Polypharmacy	64(67%)	76(70%)	59(68%)	81(70%)	67(66%)	73(72%)
Beta blockers	35(37%)	44(41%)	34(39%)	45(39%)	46(45%)	33(33%)
ACE / AT2	26(27%)	43(40%)	26(30%)	43(37%)	43(42%)	26(26%)‡
CCB	11(12%)	19(18%)	13(15%)	17(15%)	16(16%)	14(14%)
Diuretics	31(33%)	39(36%)	30(35%)	40(35%)	39(38%)	31(31%)
Nitrates	10(11%)	15(14%)	8(9%)	17(15%)	15(15%)	10(10%)

The results are reported as means ± standard deviations or numbers (percentages). OH, orthostatic hypotension; PPH, postprandial hypotension; CSH, carotid sinus hypersensitivity; age(years); BMI, body mass index(kg/m^2); SBP, systolic blood pressure(mmHg); DBP, diastolic blood pressure(mmHg); HR, heart rate(beats per minute); CIRS-G, Cumulative Illness Rating Scale for Geriatrics; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ACE/AT2, angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists; CCB, calcium channel blockers. *:significant differences ($p<0.05$) between patients with and without OH; †:significant differences ($p<0.05$) between patients with and without PPH; ‡:significant differences ($p<0.05$) between patients with and without CSH.

Measures of HRV, BPV, and BRS

No differences were found in the different measures of HRV, BPV, and BRS between patients with or without OH, PPH and CSH respectively (Table 2). Similar results were found when patients with no versus one, two or three hypotensive syndromes were compared (data not shown). Also no differences were found in the different measures of HRV, BPV and BRS between patients with or without falls, dizziness and syncope respectively (Table 3). There were also no differences between patients who presented with falls and patients who presented with syncope (data not shown).

Table 2 Comparison of Heart Rate Variability, Blood Pressure Variability and Baroreflex Sensitivity Measures Between Patients With and Without Orthostatic Hypotension, Postprandial Hypotension and Carotid Sinus Hypersensitivity

	OH–	n	OH+	n	PPH–	n	PPH+	n	CSH–	n	CSH+	n
HRV												
SDNN	60(37-86)	86	49(30-88)	93	50(27-72)	74	53(34-89)	105	56(31-90)	92	49(33-76)	87
RMSSD	51(26-86)	86	37(21-84)	93	48(23-79)	74	43(24-83)	105	51(23-89)	92	40(23-73)	87
LF	0.7(0.2-1.6)	84	0.4(0.1-2.3)	88	0.8(0.1-1.4)	71	0.4(0.2-1.7)	101	0.8(0.1-1.8)	89	0.4(0.2-1.2)	83
HF	0.7(0.1-1.9)	84	0.3(0.1-1.6)	88	0.4(0.1-2.0)	71	0.5(0.1-1.7)	101	0.6(0.1-2.6)	89	0.4(0.1-1.5)	83
LF/HF	0.9(0.7-2.0)	84	1.2(0.6-1.8)	88	1.0(0.7-2.5)	71	1.0(0.7-2.0)	101	1.0(0.7-2.3)	89	1.0(0.7-1.9)	83
BPV												
SD	11.1(8.3-13.8)	95	10.7(8.9-15.4)	108	11.5(9.0-15.2)	87	10.6(8.4-14.3)	116	11.0(8.0-14.5)	102	10.7(9.2-15.3)	101
RMSSD	6.2(4.3-8.7)	95	7.2(5.3-11.3)	108	6.6(4.7-9.3)	87	6.7(4.8-9.9)	116	6.5(4.5-9.0)	102	7.2(4.9-10.3)	101
LF	3.0(1.5-5.2)	68	3.4(1.9-7.9)	81	2.5(1.5-5.4)	67	3.5(1.9-7.6)	82	3.5(1.7-7.9)	81	2.9(1.4-5.2)	68
HF	3.2(1.7-8.3)	68	4.9(2.5-10.2)	81	3.0(1.8-7.0)	67	4.9(2.5-10.8)	82	4.5(2.1-9.8)	81	3.9(1.9-7.7)	68
BRS												
SQ+	5.5(2.4-8.2)	95	3.5(1.5-5.5)	108	3.6(1.3-7.2)	87	4.6(2.2-7.2)	116	4.9(2.2-8.3)	102	3.8(1.8-5.9)	101
SQ-	9.3(4.0-13.3)	95	7.1(3.3-11.7)	108	7.2(3.3-12.0)	87	8.4(4.2-12.1)	116	7.8(3.7-13.0)	102	7.8(3.8-11.8)	101
SD	7.7(5.1-14.3)	95	7.4(3.8-13.7)	108	7.9(4.3-14.3)	87	7.3(4.1-13.7)	116	8.3(5.2-14.0)	102	6.9(3.4-14.2)	101
LF	7.0(3.6-12.7)	50	5.7(3.5-9.0)	39	6.5(3.3-13.3)	38	6.2(3.6-9.1)	51	6.6(3.3-13.7)	42	6.1(3.7-10.2)	47
HF	7.6(4.7-15.0)	61	5.7(3.4-10.6)	56	7.0(3.2-17.4)	44	6.3(3.8-11.3)	73	6.6(3.6-15.5)	55	6.8(3.8-11.0)	62

Results are reported as medians(25^{th}-75^{th} percentiles). HRV, heart rate variability; BPV, systolic blood pressure variability; BRS, baroreflex sensitivity; SBP, systolic blood pressure; **HRV**:SDNN, standard deviation heart rate(ms); RMSSD, root mean square successive difference of heartbeats(ms); LF, low frequency power HRV($1x10^3ms^2$); HF, high frequency power HRV($1x10^3ms^2$); LF/HF, ratio of LF-HRV and HF-HRV(-); **BPV**:SD, standard deviation SBP(mmHg); RMSSD, root mean square successive difference SBP(mmHg); LF, low frequency SBP(mmHg); HF-SBP, high frequency SBP(mmHg); **BRS**:SQ+, sequence method BRS for positive sequences(ms/mmHg); SQ-, sequence method BRS for negative sequences(ms/mmHg); SD, standard deviation BRS(ms/mmHg); LF, low frequency BRS(ms/mmHg); HF, high frequency BRS(ms/mmHg).*:$p<0.01$

Table 3 Comparison of Heart Rate Variability, Blood Pressure Variability and Baroreflex Sensitivity Measures Between Patients With and Without Falls, Dizziness and Syncope

	Falls–	n	Falls+	n	Dizziness–	n	Dizziness+	n	Syncope–	n	Syncope+	n
HRV												
SDNN	50(33-111)	23	53(32-86)	155	58(37-91)	87	48(30-77)	91	51(34-84)	121	59(26-88)	57
RMSSD	44(27-89)	23	43(23-82)	155	55(28-84)	87	39(21-71)	91	45(24-82)	121	37(20-86)	57
LF	0.4(0.2-1.9)	22	0.6(0.1-1.5)	149	0.7(0.2-1.6)	84	0.4(0.2-1.6)	87	0.6(0.2-1.4)	115	0.4(0.1-1.6)	56
HF	0.4(0.2-2.0)	22	0.4(0.1-1.9)	149	0.7(0.1-1.9)	84	0.3(0.1-1.8)	87	0.4(0.1-1.6)	115	0.5(0.1-2.7)	56
LF/HF	1.2(0.6-2.5)	22	1.0(0.7-2.1)	149	1.0(0.6-2.5)	84	0.9(0.7-1.9)	87	1.0(0.7-2.1)	115	1.0(0.7-2.3)	56
BPV												
SD	11.2(7.8-16.3)	27	10.8(9.0-15.1)	175	10.8(9.2-14.1)	99	11.0(8.3-15.6)	103	11.2(9.4-14.9)	136	9.8(7.4-15.8)	66
RMSSD	6.4(3.9-8.8)	27	6.7(4.9-9.9)	175	6.6(4.9-9.2)	99	6.4(4.5-10.6)	103	6.7(4.9-9.3)	136	6.6(4.5-11.6)	66
LF	2.8(1.6-5.3)	18	3.3(1.7-6.7)	130	2.9(1.4-7.6)	71	3.4(1.9-5.9)	77	3.0(1.6-5.9)	102	4.4(1.7-9.6)	46
HF	3.2(1.7-5.9)	18	4.2(2.1-9.3)	130	4.0(1.9-8.6)	71	4.1(2.1-9.9)	77	3.9(1.9-8.6)	102	5.3(2.2-10.8)	46
BRS												
SQ+	5.2(2.4-7.8)	27	4.3(1.8-7.1)	175	3.9(1.8-7.1)	99	4.5(2.1-7.4)	103	4.4(2.1-7.1)	136	4.3(1.8-8.0)	66
SQ-	9.0(5.4-11.5)	27	7.6(3.7-12.1)	175	7.4(3.9-11.2)	99	8.6(3.7-13.3)	103	7.7(3.9-12.2)	136	8.1(3.3-11.6)	66
SD	7.6(4.2-11.7)	27	7.6(4.2-14.3)	175	7.6(4.1-14.3)	99	7.6(4.9-14.1)	103	7.2(4.1-12.8)	136	8.1(5.5-14.4)	66
LF	5.4(3.7-14.3)	14	6.6(3.5-10.2)	75	7.0(3.7-12.5)	43	5.4(3.2-10.3)	46	7.0.6(3.7-13.2)	61	5.9(3.3-9.1)	28
HF	7.4(5.2-17.9)	19	6.4(3.3-12.1)	98	6.6(3.3-13.4)	57	6.8(4.0-10.9)	60	6.8(3.7-12.2)	81	6.1(3.7-15.9)	36

Results are reported as medians(25^{th}-75^{th} percentiles). HRV, heart rate variability; BPV, systolic blood pressure variability; BRS, baroreflex sensitivity; SBP, systolic blood pressure; **HRV**:SDNN, standard deviation heart rate(ms); RMSSD, root mean square successive difference of heartbeats(ms); LF, low frequency power HRV($1x10^3ms^2$); HF, high frequency power HRV($1x10^3ms^2$); LF/HF, ratio of LF-HRV and HF-HRV(-); **BPV**:SD, standard deviation SBP(mmHg); RMSSD, root mean square successive difference SBP(mmHg); LF, low frequency SBP(mmHg); HF-SBP, high frequency SBP(mmHg); **BRS**:SQ+, sequence method BRS for positive sequences(ms/mmHg); SQ-, sequence method BRS for negative sequences(ms/mmHg); SD, standard deviation BRS(ms/mmHg); LF, low frequency BRS(ms/mmHg); HF, high frequency BRS(ms/mmHg).*:$p<0.01$

Finally, 20 patients had delayed OH, defined as onset of OH after the third minute. These patients were categorized among the "no OH" patients (n=94) in our study. Compared with the n=74 patients without OH and without delayed OH, they did not differ in HRV, BPV and BRS (data not shown).

Discussion

The main finding of this study is that there were no differences in HRV, BPV and BRS between geriatric patients with and without hypotensive syndromes. We used extensive non-invasive, easy available and state of the art indices of HRV, BPV, and BRS.(1;22-24). Most of these indices reflect primarily vagal activity, but LF-HRV and LF/HF-HRV are also thought to reflect sympathetic activity or to reflect the sympathovagal balance.(1)

Previous studies which examined the relationship between hypotensive syndromes and measures of HRV, BPV and BRS have reported conflicting results. In older persons there was an association between diminished BRS with BP fall during OH testing.(26;27) However, no difference in spectral measures of HRV and BPV was found between patients with normal and poor orthostatic tolerance.(28) During intraduodenal glucose administration for PPH testing an association between diminished BRS with SBP fall was found.(29) Spectral measures of HRV were lower(30) and systolic BPV(31) was higher in patients with versus without PPH, but the latter study could not replicate the differences in HRV measures.(31) BRS was found to be higher(8), the same(32) or lower(33) between patients with and without CSH. Spectral measures of HRV were higher in patients with CSH compared with patients without CSH.(8). In another study, no differences were found in systolic BPV measures between patients with and without CSH.(34) An explanation for these conflicting data is the difference in used methods and in diagnoses, severity of illnesses and functional capacity between study populations. Another explanation is the diversity of methods used to measure HRV, BPV and BRS in either the time or frequency domain.(35) Age-related normal values for different measures of HRV, BPV and BRS are lacking, which makes comparison between populations difficult.(1)

Our data add to the literature because for the first time all three hypotensive syndromes are meticulously characterized together in one population of consecutive older patients who visited a geriatric outpatient falls and syncope clinic. Cardiovascular autonomic dysfunction, as measured with multiple, non-invasive measures of HRV, BPV and BRS, was not a sufficient cause to explain the occurrence of these hypotensive syndromes. An explanation for our findings might lie in the fact that hypotensive syndromes, especially in the

elderly patients, are multifactorial in genesis.(36-38) The lack of an association between HRV, BPV, and BRS and hypotensive syndromes does not prove that cardiovascular autonomic control has no role in the pathophysiology of these hypotensive syndromes. However, it is unlikely that cardiovascular autonomic dysfunction is a sufficient factor, as other redundant regulatory mechanisms are able to compensate for diminished cardiovascular autonomic function and thus determine if hypotensive syndromes occur. Cardiovascular autonomic dysfunction probably is just a component cause with high frequency in geriatric patients, and therefore there is no difference to be found between these groups. The conflicting data from literature can easily be explained by the geriatric syndrome causative model, which can be filled with different combinations of factors in different subgroups.(36-39)

Strengths and Limitations

This study has some limitations. Firstly, this study was a cross-sectional analysis. Secondly, we have no complete assessment of all 14 different measures of autonomic function in all 203 patients. However, for 10 measures there is approximately 15% or less missing data, which is acceptable. Of four variables the percentage of missing data was higher because for frequency analysis consecutive data series of 50 to 100 s are necessary which was sometimes not possible because the BP measurement was interrupted by calibrations, and ECG signals were sometimes disturbed through artifacts. Moreover, the calculation of the BRS with the spectral method requires that the coherence is more than 0.5, which explains the high portion of missing data for BRS-LF and BRS-HF. Datasets of 50 to 100 s are rather short to perform frequency domain analysis in which it is advisable to have data set lengths of at least 128 consecutive beats.(40) Hereby, the estimation especially of the LF measures might be less accurate. However, despite these shortcomings, all the results of the frequency domain analysis are in line with the other determined variables of HRV, BPV, and BRS.

Thirdly, this study investigated a selective patient population, and did not have a control group. All patients were referred to an out-patient geriatric falls and syncope clinic, because of syncope, falls and/or dizziness. This has the disadvantage of a specific selection and therefore our sample is not a representative for the general population, but only for populations referred to similar outpatient clinics. On the other hand, this is the geriatric population with the highest relevance of hypotensive syndromes.

Finally, there is evidence that postural and postprandial BP responses vary during the day and therefore should be measured more than once.(12;31;41) It would be possible that we falsely classified patients to be without OH, PPH or CSH, who might in fact have the same degree of autonomic dysfunction as those

patients with OH, PPH or CSH. We found a high prevalence of syndromes, comparable to other studies, which reduces the likelihood that we missed patients. Also, when comparing patients with and without syncope or falls there still was no difference in autonomic function. Misclassification is therefore less likely.

This study has several other strengths. Firstly, the BP measurements and tests in our study were performed under standardized circumstances, with a beat-to-beat finometer (Finapres™), which is an accurate way to measure BP variability.(20)

Secondly, we limited as much as possible the confounding effects of medication on our assessment of hypotensive syndromes and on our estimates of autonomic function. To do this, all medication was withheld from midnight the night before the tests. Nonetheless, biological effects of these drugs might persist longer than the period of abstinence, especially for beta-blockers. However, in aging beta-adrenoreceptor responsiveness decreases by several mechanisms and the effects of beta-blockers are therefore less pronounced.(42) Moreover, we found no differences in the use of beta-blockers or other medication between patients with and without hypotensive syndromes, with exception of lower use of angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists in patients with CSH.

Thirdly, a strength of this study is that we investigated all three hypotensive syndromes in the same patients, where other studies only looked at one type of hypotensive syndrome.(8;26-34)

Finally, we investigated a rather large group of 203 geriatric patients on the presence of three common hypotensive syndromes, and this study addresses a potential mechanism underlying these common hypotensive syndromes.

Conclusions

In geriatric patients with hypotensive syndromes, cardiovascular autonomic function as measured by HRV, BPV, and BRS is comparable to patients without such syndromes. These findings may favor a multifactorial pathophysiology of geriatric hypotensive syndromes, and argue against a single or dominant etiological factor, that is, cardiac autonomic dysfunction. For clinical practice our data underline that in the initial diagnostic work-up of elderly patients with falls, dizziness and syncope should follow the structured approach as proposed in the evidence-based syncope guidelines, which recognizes a multifactorial etiology.(13;43)

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Chapter 2b

Syncope of unknown origin and adenosine 5'-triphosphate testing. Is there added value for geriatric patients?

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To the Editor: With interest we have read the article by Flammang et al.(1) In their well-designed, controlled trial, they show convincing evidence that cardiac pacing in individuals with syncope of unknown origin (SUO) and a positive adenosine 5′-triphosphate (ATP) test, results in fewer recurrences of syncope than those who do not receive pacing. The ATP test thus seems to be a promising additive diagnostic tool to guide the decision for pacemaker implantation.

Their study was based on a relatively small number of 88 patients with SUO who had a positive ATP test, of whom 80 patients were randomized. Patients were ineligible if they had an implantable pacemaker or defibrillator, a first-degree atrioventricular block or other sinus or atrioventricular node conduction disorder, carotid sinus hypersensitivity or diabetes mellitus. Patients with SUO with a negative ATP test were excluded. The selection process in this study raises questions. For example, it is not clear to us why 24% of the patients had diabetes mellitus, if diabetes mellitus was an exclusion criterion. In addition, this study had a very selected population of patients in whom syncope remained unexplained after the usual screening tests, including, for example, investigation of orthostatic hypotension.

We are, therefore, very interested in the flow of patients before randomization. It would be informative to place the final 80 patients in the context of the total number of patients with syncope, aged > 18 years, who visited the emergency departments or outpatient clinics of the 10 recruiting European centers between January 2000 and May 2005. In how many of those patients did the cause of syncope remain unexplained? Of these remaining patients with SUO, what was the percentage of patients who were ineligible? Among the eligible patients with SUO, what was proportion of patients with a negative ATP test? Such information can be useful in guiding the selection of the appropriate patients for pacing.

We are interested in how these results can be extrapolated to a geriatric population visiting a clinic dealing with falls and syncope. Carotid sinus hypersensitivity is present in 39% of asymptomatic older patients.(2) orthostatic hypotension and carotid sinus hypersensitivity often coexist in geriatric patients. In only one third of the patients visiting a geriatric clinic because of falls and syncope could orthostatic hypotension and carotid sinus hypersensitivity be excluded.(3) Furthermore, extrapolation to geriatric patients is difficult because syncope in geriatric patients is often not due to a single cause but multiple causes.(4,5) Syncope is due to a combination of age-related physiologic changes and comorbidities. Factors such as multifactorial causality, the lack of witnesses, and the overlap between falls and concomitant cognitive impairment all make it difficult to attribute a single diagnosis to an episode of syncope.(4)

Flammang et al.(1) provide convincing evidence for an effective diagnostic tool and therapy in patients with SUO. However, in our opinion, the added value in clinical practice for a geriatric population dealing with falls and syncope has to be further established.

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Chapter 3a

Diastolic blood pressure drop after standing as a clinical sign for increased mortality in older falls clinic patients

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Abstract

Background

Orthostatic hypotension, postprandial hypotension, and carotid sinus hypersensitivity are hypotensive syndromes with high prevalence in older people. However, their pathophysiology and prognostic significance remain largely unknown.

Methods

In a retrospective cohort study of 313 consecutive patients visiting our falls outpatient clinic, we examined the clustering of orthostatic hypotension, postprandial hypotension, and carotid sinus hypersensitivity in the same patients, which might reflect a shared similar pathophysiology. The value of hypotensive syndromes presence and the degree of blood pressure decline as prognostic indicators for mortality was assessed using Cox proportional hazards analyses.

Results

In 313 patients (mean age 78.7±8.0 years), 168 of 309 (54%), 175 of 302 (58%), and 143 of 272 (53%) were diagnosed with orthostatic hypotension, postprandial hypotension, and sinus carotid hypersensitivity, respectively. There was no clustering of the hypotensive syndromes. During a median follow-up of 23.0 months, 58 (19%) patients died. Orthostatic hypotension, but not postprandial hypotension or carotid sinus hypersensitivity, predicted mortality (hazard ratio: 1.97; 95% confidence interval: 1.11-3.47). After adjusting for age, co-morbidity and other baseline characteristics, this relationship was no longer significant. However, orthostatic hypotension with severe diastolic blood pressure decline of ≥20 mmHg remained a powerful independent predictor of mortality (hazard ratio: 2.50; 95% confidence interval: 1.20-5.22).

Conclusions

In falls clinic patients, hypotensive syndromes did not cluster and did not independently predict mortality. However, orthostatic hypotension with severe diastolic blood pressure decline was a powerful independent predictor of mortality and might be used prognostically as an easily available cardiovascular sign of increased mortality risk.

Introduction

Orthostatic hypotension (OH), postprandial hypotension (PPH), and carotid sinus hypersensitivity (CSH) are disorders of blood pressure (BP) regulation with high prevalence in the elderly.(1-15) Structural and functional changes in the cardiovascular system and its neurohormonal regulation are associated with aging, may compromise BP homeostasis (4), and give rise to each of these hypotensive syndromes. We therefore hypothesised that hypotensive syndromes share a similar pathophysiology, resulting in the clustering of these three syndromes in the same persons.

Hypotensive syndromes are of clinical importance because they can cause fall-related injuries, limit the quality of life, and impede relevant treatment of concomitant diseases, such as hypertension or heart failure.(3,16) As such these syndromes may be indicators for frailty in the elderly population.(17) Despite their importance, relatively little is known about the prognostic aspects of these syndromes in older patients. In middle-aged patients, OH predicts all-cause mortality.(2,3,8,18) In older patients, an association between OH and mortality has been reported (6-8,12), but the results seem inconsistent.(6,15,19-21) Similarly, relatively little is known about PPH and CSH as predictive indicators of mortality, and results from previous studies do not show consistent results.(1,4,11,22) The observed mortality may be a consequence of aging with underlying cardiovascular disease, and the hypotensive syndromes may be no more than a reflection of this cardiovascular disease. On the other hand, mortality may also be caused by harmful effects of hypotensive syndromes through hypoperfusion of organs. Hypotensive syndromes are associated with myocardial infarction (23,24), stroke (25) and falls and related injuries.(15)

Definitions of hypotensive syndromes are dichotomous in nature. In addition to the presence of hypotensive syndromes, the amount of BP decline in response to a stimulus also may play an important role in mortality. A severe drop in BP might reflect a more compromised cardiovascular system and higher risk for serious complications, such as myocardial infarction, stroke and fall-related injury.

We hypothesised that hypotensive syndromes are predictors for all-cause mortality in a geriatric population and that there is a dose–effect relationship between the amount of BP decline during testing for hypotensive syndromes and mortality. This might be important in the selection of older patients for cardiological and cardiosurgical procedures. Recently, frailty has been shown to be a predictor of outcome in elderly patients who underwent cardiac surgery.(26)

Methods

Study population

This retrospective study included 313 consecutive patients who were referred to the geriatric outpatient falls clinic of the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, from May 2005 to June 2010 because of a fall, dizziness or syncope and who were able to undergo the test protocol for investigation of the presence of OH, PPH and CSH. The patients were judged able to undergo the test protocol if they were able to follow the instructions, could stand for 10 minutes and could drink a test meal of 200 ml within 10 minutes. This test protocol is part of the standard care for patients who visit the geriatric outpatient fall clinic and conformed to the Declaration of Helsinki. Patients received targeted multifactorial interventions as standard medical care, which among others consisted of medication review with starting and/or stopping of medications, prescription of walking aids, and education on lifestyle factors and how to influence them.

Test protocol

Before OH, PPH and CSH testing, the patients underwent a complete physical examination including medical history. Baseline characteristics (age, gender, body mass index (BMI)), baseline systolic BP (SBP), diastolic BP (DBP), medical history and medication use were documented. The presence and severity of co-morbidity was recorded using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).(27) This scale estimates the illness burden and diversity using a five-point scale (0-4, with higher scores indicating more severe morbidity) reflecting the severity of pathology in each of 14 categories (maximum total score: 56). The CIRS-G score was used to compare the co-morbidity between groups. The patients fasted overnight, and medication was withheld from midnight the night before. All tests were performed by a physician's assistant in the morning or afternoon. During the tests, BP and heart rate were constantly measured using a beat-to-beat Finometer (Finapres^{TM})(28) and a three-lead electrocardiogram (ECG). BP was measured at the non-dominant arm, which was held at heart level with a sling. Before testing and at each time point during the tests (OH test every minute, PPH test every 5 minutes), BP and heart rate were documented. The reported BP values were averages of 20 heart beats (10 before and 10 after each time point). For OH and PPH testing, SBP and DBP values were determined. For CSH, BP values were determined by averaging the values of three heart beats around the lowest BP value during carotid sinus massage (CSM) or in a 30-second period after CSM. From the ECG registration, the R-R interval before and the longest interval during or in a 30-second period after

CSM were documented. All test results were electronically recorded in a database after approval of the test performance.

Orthostatic hypotension test

After a 10-minute resting period in the supine position, the patients were asked to stand up and remain standing for ten minutes. Baseline values of BP and heart rate were defined as the average during the 60 seconds before rising. OH was defined as a SBP decline of 20 mmHg or more or a DBP decline of 10 mmHg or more within 3 minutes of standing from supine.(29)

Postprandial hypotension test

The patients were asked to drink a test meal within 10 minutes in the sitting position. The test meal was a solution of 100 ml glucose syrup and 100 ml lactose-free milk containing 292 kcal, 65 g carbohydrates, 2 g fat and 4 g protein. The meal temperature was 20-25ºC.(30) After drinking the meal, BP and heart rate were monitored over 75 minutes. PPH was defined as a SBP decline of 20 mmHg or more within 75 minutes after a meal.(1,11)

Carotid sinus massage

CSM was performed in the supine position after 5 minutes of rest. Firm, longitudinal massage was performed for 5 seconds over the site of maximal pulsation of the right carotid artery and repeated on the left side when the SBP and heart rate were normalised. If no significant response in heart rate or SBP was obtained with supine CSM, the procedure was repeated with the patient tilted at 70º on a tilt table with footplate.(31) Accepted contraindications were taken as exclusion criteria for CSM: a murmur over the carotid artery, myocardial infarction, cerebral ischemia in the past 3 months, or a history of ventricular tachyarrhythmia's.(31) CSH was defined as an interruption of heart rate over at least three seconds (cardio-inhibitory type), as a decrease of SBP of 50 mmHg or more (vasodepressor type) or as a combination of both (mixed type).(29,32)

All-cause mortality

The follow-up period ended on August 2010. Data on vital status were ascertained through linkages with the Dutch municipal administration. When the municipal administration could not provide this information, the general practitioner or the patient's family was contacted. For one patient, the exact date of death was not discovered, and another patient was lost to follow-up because of emigration. From these two patients, the year and month of death and emigration were known. For survival analysis, we used the month as the unit of time; therefore, follow-up was complete for all patients, including the two patients mentioned above.

Statistical analysis

Characteristics of the patients according to presence of BP syndromes (yes or no) were compared using an unpaired t-test and chi-squared (χ^2) statistics. The results are presented as the means ± standard deviations (SD) or percentages unless otherwise stated. Clustering of BP syndromes was tested with chi-squared (χ^2) statistics.

Cox proportional hazards models were used to identify whether OH, PPH and CSH status predicted mortality. The first model was unadjusted, and the second model was adjusted for age, gender, BMI, co-morbidity (CIRS-G score), medication use and baseline SBP and DBP. For medication use, we used the following medication groups: 1) beta blockers; 2) calcium channel blockers; 3) diuretics; 4) angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists; 5) nitrates; 6) platelet aggregation inhibitors; 7) cholesterol-lowering drugs, i.e., 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) or fibrates; 8) psychiatric medication, i.e., antidepressants, antipsychotics and anxiolytics; and 9) medication for Parkinson's disease or parkinsonism.
To examine the influence of specific disease profiling in comparison with the CIRS-G score, we repeated the adjusted second model with specific disease information from the medical histories instead of the CIRS-G scores. We used the following disease groups: 1) dementia; 2) depression or anxiety disorder; 3) chronic obstructive pulmonary disease; 4) diabetes mellitus; 5) Parkinson's disease or disorders with parkinsonism; 6) the cardiovascular disease group, including myocardial infarction, angina pectoris, heart failure, peripheral vascular disease, aneurysm of the aorta, stroke, and transient ischemic attack; 7) hypertension; and 8) malignancy.

The results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Because of the frequent co-existence of multiple hypotensive syndromes in the same patient, we also performed unadjusted and adjusted Cox proportional hazards analyses of patients with no versus one, two or three hypotensive syndromes and patients with no versus at least one hypotensive syndrome.

To investigate the dose–effect relationship between mortality and the amount of BP decline during testing for hypotensive syndromes, SBP and DBP decline were divided into three subgroups (mild, moderate and severe) for each hypotensive syndrome. The patients were classified into the mild subgroup if they did not meet the BP criteria for the different hypotensive syndromes. For OH and PPH, the mild, moderate and severe SBP decline subgroups were defined as a decline of < 20 (no OH or PPH), 20 to 35, and ≥ 35 mmHg. The mild, moderate and severe DBP decline subgroups for OH were defined, respectively, as a decline of < 10 (no OH), 10 to 20, and ≥ 20 mmHg. The same subgroup

classification as OH was used for DBP decline in PPH. DBP decline is not a criterion for PPH, but a DBP decline subgroup classification was used analogous to the same SBP decline criterion in both OH and PPH. For CSH, the mild, moderate and severe SBP decline subgroups were defined, respectively, as a decline of < 50 (no CSH), 50 to 65 and ≥ 65 mmHg. Because DBP decline also is not a criterion for CSH and the DBP decline was expected to be larger than that in OH or PPH, the following DBP decline subgroup classification was used in CSH: < 15, 15 to 25 and ≥ 25 mmHg. To investigate the relationship between mortality and mild, moderate and severe decline of SBP and DBP during BP tests, Cox proportional hazards models were repeated with and without adjustment for age, gender, BMI, co-morbidity (CIRS-G score), medication use and baseline SBP and DBP. In the adjusted analysis, we also studied the influence of specific disease profiling in comparison with the CIRS-G score by repeating the adjusted second model with specific disease information from the medical histories instead of the CIRS-G scores. The results were considered to be significant for p-values < 0.05. The results were expressed as HRs with 95% CIs. All analyses were performed using SPSS software version 16 for windows (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

Figure 1 shows the flow chart of the tested patients. Of the 313 patients, 309, 302 and 272 completed the tests for OH, PPH and CSH, respectively. Of these patients, 54%, 58% and 53% were diagnosed with OH, PPH and CSH, respectively. Of the 143 patients with CSH, 53% had the CSH vasodepressor subtype, 11% had the cardio-inhibitory subtype and 36% had both subtypes. Missing values for OH (n = 4) and PPH (n = 11) tests were due to unreliable measurements. CSM was not performed in 41 (13%) patients because they met the exclusion criteria. In total, 261 (83%) patients completed all three tests. Of these patients, 33 (13%) had no hypotensive syndrome, and thus, 228 (87%) patients had at least one or more hypotensive syndromes. The distribution of the patients diagnosed with one or more hypotensive syndromes is shown in Figure 2.

Table 1 compares the demographic and clinical characteristics of the patients with and without OH, PPH and CSH. Compared with the patients without OH, the patients diagnosed with OH were older, had lower BMIs, were more frequently female, had higher mean baseline SBPs and DBPs, and used more angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists. The patients with PPH were also older, had higher baseline SBPs and had more

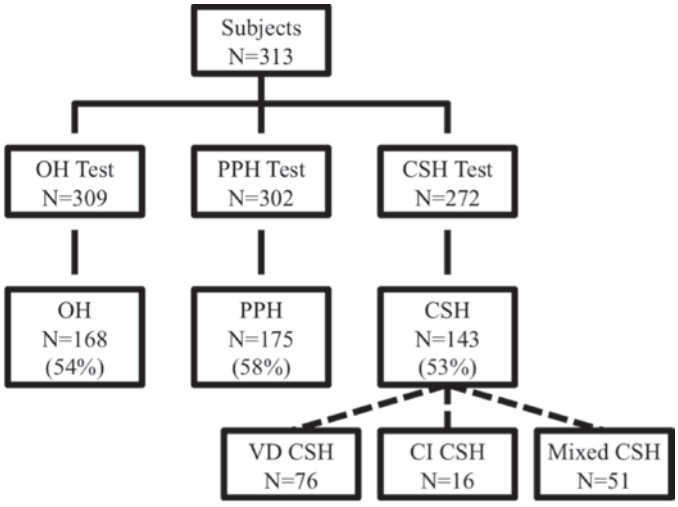

Figure 1 Flow chart of the tested patients

OH, orthostatic hypotension; PPH, postprandial hypotension; CSH, carotid sinus hypersensitivity; VD, vasodepressor; CI, cardio-inhibitory.

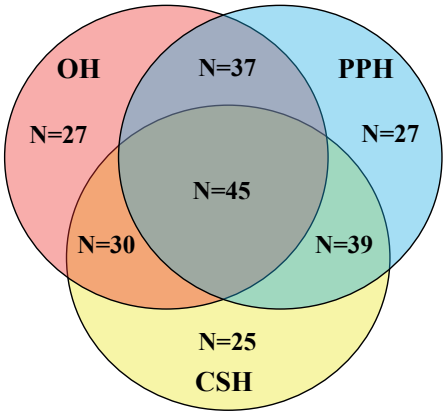

Figure 2 Venn diagram of the number of patients (n = 230) with one or more hypotensive syndromes

OH, orthostatic hypotension; PPH, postprandial hypotension; CSH, carotid sinus hypersensitivity. The patients (n = 33) with no hypotensive syndrome and those (n = 50) who did not receive all tests were omitted from this figure.

Table 1 Comparison of the baseline demographic and clinical characteristics of the patients with and without OH, PPH and CSH

Variable	OH– (n = 141)	OH+ (n = 168)	PPH– (n = 127)	PPH+ (n = 175)	CSH– (n = 127)	CSH+ (n = 143)
Age	77.3 ± 8.7	79.7 ± 7.2*	76.7 ± 8.3	79.8 ± 7.6†	77.1 ± 9.1	78.9 ± 6.9
BMI	27.1 ± 4.5	25.9 ± 4.3*	26.9 ± 4.5	26.2 ± 4.4	27.2 ± 4.7	25.8 ± 4.0‡
Female, n (%)	79 (56%)	117 (70%)*	83 (65%)	108 (62%)	77 (61%)	88 (62%)
Baseline SBP	163 ± 26	174 ± 27*	159 ± 21	175 ± 28†	164 ± 25	171 ± 26‡
Baseline DBP	77 ± 12	80 ± 12*	78 ± 12	79 ± 12	78 ± 12	80 ± 12
CIRS-G total score	10.9 ± 4.7	11.8 ± 4.5	10.9 ± 4.6	11.7 ± 4.5	11.1 ± 4.7	11.3 ± 4.6
Medical history						
Dementia	10 (7%)	13 (8%)	7 (6%)	14 (8%)	8 (6%)	12 (8%)
Depression or anxiety	23 (16%)	33 (20%)	28 (22%)	28 (16%)	24 (19%)	26 (18%)
COPD	26 (18%)	30 (18%)	20 (16%)	33 (19%)	21 (17%)	24 (17%)
Diabetes mellitus	30 (21%)	28 (17%)	18 (14%)	40 (23%)	25 (20%)	22 (16%)
Parkinson(ism)	6 (4%)	10 (6%)	4 (3%)	10 (6%)	8 (6%)	7 (5%)
CVD	50 (36%)	76 (45%)	42 (33%)	80 (46%)†	48 (38%)	53 (37%)
Hypertension	68 (48%)	77 (46%)	51 (40%)	91 (52%)†	68 (54%)	56 (39%)‡
Malignancy	21 (15%)	39 (23%)	23 (18%)	38 (22%)	23 (18%)	29 (20%)
Medication use						
Beta blockers	55 (39%)	64 (38%)	47 (37%)	67 (38%)	55 (43%)	46 (32%)
CCB	16 (11%)	31 (19%)	21 (17%)	25 (14%)	21 (17%)	18 (13%)
Diuretics	50 (36%)	65 (39%)	47 (37%)	67 (38%)	49 (39%)	46 (32%)
ACE/AT2	38 (27%)	71 (42%)*	38 (30%)	67 (38%)	48 (38%)	41 (29%)
Nitrates	17 (12%)	18 (11%)	12 (9%)	21 (12%)	15 (12%)	13 (9%)
PAI	56 (40%)	68 (41%)	50 (39%)	71 (41%)	50 (39%)	56 (39%)
Statins/fibrates	46 (33%)	39 (23%)	36 (28%)	46 (26%)	26 (21%)	48 (34%)‡
Psychiatric drugs	61 (43%)	71 (42%)	51 (40%)	67 (38%)	51 (40%)	53 (37%)
Anti-Parkinson drugs	2 (1%)	8 (5%)	3 (2%)	6 (3%)	5 (4%)	4 (3%)

The results are reported as the means ± standard deviations or frequencies. OH, orthostatic hypotension; PPH, postprandial hypotension; CSH, carotid sinus hypersensitivity; age in years; BMI, body mass index in kg/m^2; SBP, systolic blood pressure in mmHg; DBP, diastolic blood pressure in mmHg; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CCB, calcium channel blockers; ACE/AT2, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists; PAI, platelet aggregation inhibitors. * Indicates significant differences ($p < 0.05$) between patients with and without OH; † indicates significant differences ($p < 0.05$) between patients with and without PPH; ‡ indicates significant differences ($p < 0.05$) between patients with and without CSH.

prior cardiovascular disease and hypertension. The patients with CSH had lower BMIs, higher baseline SBPs, less prior hypertension and used more cholesterol-lowering drugs compared with those without CSH.

Clustering of hypotensive syndromes

able 2 shows the presence of other hypotensive syndromes in the patients with or without a certain index hypotensive syndrome. There was no clustering of hypotensive syndromes. Thus, PPH and CSH were not more prevalent in the patients with OH than in the patients without OH. Likewise, OH and CSH were not more prevalent in the patients with PPH than in the patients without PPH. The same was true for the prevalence of OH and PPH in patients with and without CSH.

Table 2 Clustering of OH, PPH and CSH

Variable	OH– (n = 141)	OH+ (n = 168)	PPH– (n = 127)	PPH+ (n = 175)	CSH– (n = 127)	CSH+ (n = 143)
Diagnosis of OH, n (%)	---	---	63 (50%)	99 (57%)	65 (51%)	77 (54%)
Diagnosis of PPH, n (%)	74 (52%)	99 (59%)	---	---	65 (51%)	85 (59%)
Diagnosis of CSH, n (%)	65 (46%)	77 (46%)	55 (43%)	85 (49%)	---	---

OH, orthostatic hypotension; PPH, postprandial hypotension; CSH, carotid sinus hypersensitivity.

All-cause mortality

During the median follow-up period of 23.0 months (range 1 to 61 months), 58 patients (19%) died. The risk of mortality was higher in the patients with OH than in the patients without OH (HR = 1.97; 95% CI 1.11-3.47). After adjustment for age, gender, BMI, co-morbidity (CIRS-G score), medication use and baseline SBP and DBP, the association was no longer significant (p = 0.30). Neither PPH nor CSH was significantly associated with mortality in the unadjusted or adjusted model (Table 3). The unadjusted and adjusted analysis of the patients with no versus one, two or three hypotensive syndromes and the patients with no versus at least one hypotensive syndrome did not reveal a significant difference in mortality. Adjustment for specific diseases instead of the CIRS-G scores did not alter the adjusted analysis.

BP decline and mortality

Table 4 shows the adjusted HRs for the different SBP and DBP decline subgroups during testing for the different hypotensive syndromes (there was no essential

Table 3 Cox proportional hazards analysis for all-cause mortality related to blood pressure syndromes

Parameter	Hazard ratio	95% Confidence interval	P-value
OH, unadjusted	1.97	1.11-3.47	0.02
OH, adjusted*	1.39	0.75-2.58	0.30
PPH, unadjusted	1.40	0.79-2.50	0.24
PPH, adjusted*	1.04	0.57-1.90	0.91
CSH, unadjusted	0.85	0.45-1.60	0.62
CSH, adjusted*	0.93	0.47-1.83	0.83

OH, orthostatic hypotension; PPH, postprandial hypotension; CSH, carotid sinus hypersensitivity. *Adjusted for age, gender, body mass index, co-morbidity, medication use and baseline systolic and diastolic blood pressure.

difference compared with the unadjusted HRs). The survivals of the moderate and severe SBP decline subgroups during OH, PPH and CSH testing were not significantly different from the mild SBP decline subgroup. The same was true for the survival of the moderate and severe DBP decline subgroups during PPH and CSH testing. However, survival was significantly lower in the patients with a severe DBP decline (≥ 20 mmHg) during the OH test than in the other two subgroups after adjustment for age, gender, BMI, co-morbidity (CIRS-G score), medication use and baseline SBP and DBP (Figure 3; HR: 2.50; 95% CI: 1.20-5.22). Adjustment for specific diseases instead of the CIRS-G score did not alter the adjusted analysis.

Discussion

The main finding of this study was that hypotensive syndromes did not cluster and did not independently predict mortality. OH was a predictor of mortality; however, after adjustment for covariates, OH did not remain an independent predictor of mortality. Nevertheless, in these geriatric patients, OH with a severe decline in DBP was a powerful independent predictor of mortality.

In our study, the hypotensive syndromes often occurred together. Fifty-seven per cent of the patients had at least two syndromes or more. This was in accordance with other studies that also have shown that OH and PPH or OH and CSH frequently occurred together in the same geriatric patient.(13,33-37) In the patients with OH, the other hypotensive syndromes were not more prevalent than in the patients without OH. The same was true for the patients with PPH or CSH. This absence of clustering of hypotensive syndromes in the same patients

Table 4 Cox proportional hazards analysis for all-cause mortality related to systolic and diastolic blood pressure decline during testing for OH, PPH and CSH

Category	Subgroup	N	Hazard ratio	95% Confidence interval	P-value
OH, SBP decline*	Mild (< 20 mmHg)	166	1	--	--
	Moderate (20-35 mmHg)	72	1.42	0.71-2.83	0.32
	Severe (≥ 35 mmHg)	69	1.29	0.67-2.51	0.45
OH, DBP decline*	Mild (< 10 mmHg)	186	1	--	--
	Moderate (10-20 mmHg)	84	0.96	0.49-1.87	0.90
	Severe (≥ 20 mmHg)	37	2.50	1.20-5.22	0.01
PPH, SBP decline*	Mild (< 20 mmHg)	126	1	--	--
	Moderate (20-35 mmHg)	92	1.06	0.52-2.13	0.88
	Severe (≥ 35 mmHg)	80	1.04	0.50-2.14	0.92
PPH, DBP decline*	Mild (< 10 mmHg)	95	1	--	--
	Moderate (10-20 mmHg)	132	1.17	0.59-2.32	0.66
	Severe (≥ 20 mmHg)	71	0.80	0.36-1.79	0.59
CSH, SBP decline*	Mild (< 50 mmHg)	142	1	--	--
	Moderate (50-65 mmHg)	70	0.40	0.13-1.19	0.10
	Severe (≥ 65 mmHg)	56	0.89	0.36-2.20	0.79
CSH, DBP decline*	Mild (< 15 mmHg)	60	1	--	--
	Moderate (15-25 mmHg)	136	0.59	0.27-1.30	0.19
	Severe (≥ 25 mmHg)	72	0.59	0.22-1.60	0.30

OH, orthostatic hypotension; PPH, postprandial hypotension; CSH, carotid sinus hypersensitivity; HR, hazard ratio; ref, reference. *Adjusted for age, gender, body mass index, co-morbidity, medication use and baseline systolic and diastolic blood pressure.

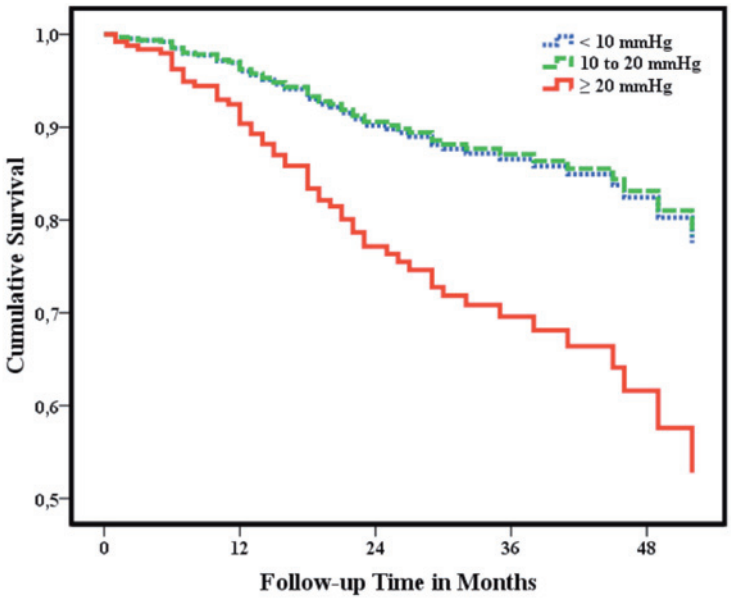

Figure 3 Cox proportional hazards cumulative survival curves with respect to DBP decline during OH test adjusted for age, gender, BMI, co-morbidity, medication use and baseline SBP and DBP

DBP, diastolic blood pressure; OH, orthostatic hypotension; BMI, body mass index; SBP, systolic blood pressure.

suggested different underlying pathophysiological mechanisms for the different hypotensive syndromes. These results corresponded with those of other studies that have shown no basis for a common mechanism between OH and CSH (37) and that patients with PPH were not necessarily also at risk for development of OH.(13,36)

Previous studies that have examined the relationship between OH, PPH or CSH and mortality have reported conflicting results. An explanation for this is the difference in populations that were studied. In middle-aged community-dwelling individuals, OH has been shown to predict mortality.(3,8) It is difficult to compare studies that have investigated mortality in older people because they had a high diversity in diagnoses, severity of illnesses and functional capacity. (38) OH was found to predict mortality in older people from Finland (6) and older Japanese men.(7) However, other studies have found no impact of OH on mortality in older people (4,20,21) and patients discharged from acute geriatric wards.(15)

In the present study, there was no dose–response relationship between change in SBP and mortality in the different BP syndromes. Fisher et al.(4) found a dose–response relationship between a drop in SBP during PPH and mortality in low-level care residents, but this relationship was not adjusted for possible confounders. Aronow et al. (1) found that the mean maximal decrease in SBP during PPH was an independent predictor for mortality in older nursing home residents. These different results might be explained by the different populations studied, residents versus outpatient clinic visitors and possibly by the higher number of frail individuals in institutionalised populations compared with the general population. The only study on mortality and CSH did not investigate a dose response.(22) Several studies have found a dose–response relationship between decline in SBP and DBP during OH and vascular-related or all-cause mortality.(3,6,7) In our study during OH testing, a severe decline in DBP, but not SBP, increased all-cause mortality. A possible explanation might be that the excess mortality was caused by myocardial ischemia. DBP reductions, but not SBP reductions, have been associated with an increased risk of myocardial infarction.(23) In another study, only diastolic OH predicted coronary events.(3) The link between DBP drop and myocardial infarction may be related to the crucial role of diastolic blood flow on myocardial perfusion.(23)

Strengths and limitations

The present study has several strengths. First, the follow-up in our study was complete. Second, the BP measurements and tests in our study were performed under standardised circumstances with a beat-to-beat Finometer (Finapress™), which is an accurate way to measure BP variability.(28) Additionally, the exclusion of tests because of unreliable measurements was rarely required.

Third, co-morbidity was documented very thoroughly. The patients underwent full geriatric assessments with thorough anamnesis, hetero-anamnesis, physical examination, medical history and medication use. Co-morbidity was documented with the CIRS-G. The CIRS-G is frequently used in other studies, and good reliability and validity have been proven.(27,39) The advantage of using this method is that it registers not only the number of illnesses but also the severity of illnesses. Adjustment for specific diseases instead of the CIRS-G scores did not alter the results. Fourth, we included medication groups in our analysis, which could have influenced either mortality or the occurrence of hypotensive syndromes or both. Medication was withheld from midnight the night before the test, so only long-acting drugs possibly influenced our measurements. Finally, a strength of this study was that all three hypotensive syndromes in the same patients were investigated to determine their impact on mortality. Most studies have investigated only the relationship between one

hypotensive syndrome and mortality.(1,3,6-8,12,15,22) In one study, the influence of PPH and OH on all-cause mortality in older low-level care residents and PPH, but not OH, was found to be an independent predictor of all-cause mortality.(4)

The present study has some limitations. First, this study was a retrospective analysis, and its accuracy depended on the availability of information within the medical records. The patients received a multifactorial intervention, which could have influenced mortality. However, a systematic review and meta-analysis showed no influence of multifactorial intervention on mortality among older people in community and emergency care settings.(40) Thus, although unlikely, we cannot completely rule out that our results may have been confounded by these multifactorial interventions. Second, we analysed all-cause mortality but not cause-specific mortality, such as cardiovascular mortality, because it was impossible to reliably determine the cause of death for many patients. In older people, the cause of death is often unclear or related to multiple problems and thus, it is hard to assess validly without post-mortem data. It would be interesting to determine if the presence of hypotensive syndromes influenced the risk of hospitalisation or falls. However, it was impossible to reliably determine falls or hospitalisation for many patients in this retrospective analysis. Third, our results apply to a selection of patients who were referred to our falls clinic. Because of potential referral bias, our results may not be externally valid to the general population of elderly patients who have fallen. Fourth, the BP measurements were performed once, in the morning or afternoon. There is evidence that postural and postprandial BP responses vary during the day and therefore should be measured more than once.(14,41) However, there is also evidence that OH is more prevalent in the morning and afternoon than in the evening.(14,41) PPH is also more prevalent, more severe and more frequently symptomatic after breakfast and lunch than after diner.(36,42) The prevalences of the hypotensive syndromes found in our study were therefore not underestimated and probably accurate. Finally, it is difficult to control for all confounding factors in a single study. Some residual confounding may have persisted.

Conclusions

In falls clinic outpatients, hypotensive syndromes did not cluster and did not independently predict mortality. However, OH with severe DBP decline may be a powerful independent predictor of mortality and may be used prognostically as an easily available cardiovascular sign for increased mortality risk in older falls clinic patients.

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Chapter 3b

Prognostic significance of blood-pressure variability

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To the Editor: Peter Rothwell and colleagues(1) provide convincing evidence that visit-to-visit blood-pressure variability is a strong predictor of stroke, independent of mean systolic blood pressure. Although they do not point at a pathophysiological explanation, we would like to add that cerebrovascular reactivity is the complementary part of blood-pressure variability with regard to incident cerebral ischaemia,(2) and that these entities together require further investigation. Unfortunately, visit-to-visit heart rate variability contained no prognostic information about stroke occurrence. However, non-linear heart rate variability, rather than the traditional variability, is able to capture the long-range correlation that may still have prognostic value.(3) A drawback of use of blood-pressure variability in routine clinical management of hyper tension is that obtaining it requires several visits. One option to solve this is to observe variability in both blood pressure and heart rate continuously and non-invasively over some time (eg, 5–10 min) before the visit to allow direct incorporation of blood-pressure variability in hypertension management.(4) As mentioned by Rothwell and colleagues, the postural change in blood pressure, but also the less well studied postprandial change in blood pressure, may contain additional prognostic information about blood pressure regulation.(5) This study justifies a plea for clinicians and researchers to put more focus on the dynamics of cardio vascular and cerebrovascular regulation, especially in older people because of the high prevalence of vascular events, the lack of predictive value of the classic risk factors (eg, cholesterol, hypertension) in old age, and because the predictive value of visit-to-visit blood-pressure variability decreases substantially with age.

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Chapter 3c

Early postural blood pressure response and cause-specific mortality among middle-aged adults: what is the role of diastolic blood pressure?

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To the Editor: With interest we have read the article by Fedorowski et al.(1), which provides valuable information about cause-specific mortality in middle-aged subjects with orthostatic hypotension. In their study orthostatic hypotension (defined as a decrease in systolic blood pressure ≥20 mmHg and/or decrease in diastolic blood pressure ≥10 mmHg within three minutes of standing) was associated with mortality through injuries and neurologic diseases. Our major comment is that the article lacks data on the postural diastolic pressure response, both in describing the whole group with orthostatic hypotension, and the analyses of all cause and cause-specific mortality.

Surprisingly, orthostatic hypotension and postural systolic blood pressure decline was not associated with cardiovascular mortality, although there was such an association in a smaller rescreened subsample. In other studies orthostatic hypotension was associated with myocardial infarction in middle-aged adults(2) and home dwelling elderly(3). Unfortunately Fedorowski et al.(1) did not study the influence of postural diastolic blood pressure decline on cause-specific mortality. There might be a crucial role of diastolic blood flow on myocardial perfusion and subsequently myocardial infarction and cardiovascular mortality. (3) Postural diastolic, but not systolic blood pressure decline, seems to be associated with an increased risk of myocardial infarction.(3) Moreover, in the same study population of the Malmö Preventive Project already the association was found that postural diastolic, but not systolic blood pressure decline predicts coronary events.(4)

In conclusion, Fedorowski et al.(1) added very valuable information to the current knowledge of orthostatic hypotension through information on cause-specific mortality. However, we miss in their study specific data on cause-specific mortality in relation to postural diastolic blood pressure decline and especially regarding cardiovascular mortality.

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Chapter 4

Impaired systolic blood pressure recovery directly after standing predicts mortality in older falls clinic patients

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Abstract

Background

Normally, standing up causes a blood pressure drop within 15 seconds, followed by recovery to baseline driven by blood pressure control mechanisms. The prognostic value of this initial blood pressure drop, but also of the recovery hereafter, is unknown. The aim of this study was to examine the prognostic value of these blood pressure characteristics in response to standing.

Methods

In a retrospective cohort study of 238 consecutive patients visiting our falls outpatient clinic, we examined the relation between all-cause mortality and blood pressure decline and recovery directly after active standing up with Cox proportional hazards analyses.

Results

Of 238 patients (mean age 78.4±7.8 years), during a median follow-up of 21.0 months, 36(15%) patients died. Neither absolute nor relative (%) initial blood pressure drop after standing predicted mortality. In contrast, the magnitude of blood pressure recovery 40 to 60 seconds after standing was associated with mortality, even after adjustment for age, co-morbidity and other baseline characteristics. When systolic blood pressure had recovered to less than 80% of pre-standing baseline after 60 seconds of standing, this was a powerful independent predictor of mortality (hazard ratio:3.00;95% confidence interval: 1.17-7.68).

Conclusions

Failure to recover from blood pressure decline in the first minute after active standing up is associated with excess mortality in falls clinic patients. A recovery of systolic blood pressure to less than 80% of baseline after 60 seconds may be used as an easy available cardiovascular marker for increased mortality risk in older falls clinic patients.

Introduction

The blood pressure (BP) response after standing up has two main components. The first component is a BP decline (often preceded by a small transient initial increase in BP, possibly due to leg and abdominal muscle tensing) within the first 15 seconds due to a mismatch in blood volume entering and leaving the arterial vasculature. Upon standing, cardiac output increases due to the shift of blood to the thorax as a consequence of compression of leg and splanchnic venous vessels(1-3). However, despite this increase in cardiac output, BP decreases -after the transient small rise- because total peripheral resistance is reduced to a further degree than cardiac output is increased, due to instantaneous vasodilatation in the active leg muscles.(1,4-8) After about 15 seconds the second component follows, and this is the recovery of BP by counteracting regulatory mechanisms of the arterial baroreflex.(3)

Regarding the first component, when the initial drop in BP is severe, this may pose a risk of serious complications, such as falls, fall-related injury, syncope and directly or indirectly myocardial infarction, stroke and even mortality.(9-11) Pathophysiologically, these negative outcomes can be related to insufficient perfusion of the brain and the myocardium.

For the second component, an impaired recovery of BP after standing prolongs this state of insufficient perfusion of vital organs. In addition, impaired recovery of BP after standing may reflect compromised cardiovascular control, and may be an indication of underlying disease. The prognostic meaning of these two components of the BP response after standing (i.e drop and recovery) are unknown. Recovery patterns of systolic BP (SBP) after standing have been studied but did not show an association with falls and frailty(12), however the relation of these patterns with mortality has not been studied. We hypothesized that both the severity of BP decline after standing and the level of impairment of the BP recovery hereafter are associated with all-cause mortality in a geriatric population.

Methods

Study population

This retrospective study included 313 consecutive patients who were referred to the geriatric outpatient falls clinic of the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, from May 2005 to June 2010. Patients were referred because of a fall, dizziness or syncope. All patients were tested with a standing up test. This was part of a standardized diagnostic test protocol which

has been described in detail elsewhere.(13) According to the Declaration of Helsinki informed consent was asked verbally prior to the tests.

Baseline assessment

Patients underwent a complete medical history and physical examination before testing. Baseline characteristics (age, gender, body mass index (BMI), SBP, diastolic BP (DBP), heart rate, medical history and medication use) were documented. The presence and severity of co-morbidity was recorded using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G, ranging 0-56).(14)

We categorized medical history in the following disease groups: 1) dementia; 2) depression or anxiety disorder; 3) chronic obstructive pulmonary disease; 4) diabetes mellitus; 5) Parkinson's disease or disorders with parkinsonism; 6) the cardiovascular disease group, including myocardial infarction, angina pectoris, heart failure, peripheral vascular disease, aortic aneurysm, stroke, and transient ischemic attack; 7) hypertension; and 8) malignancy.

For medication use the following medication groups were used: 1) beta-blockers; 2) calcium-channel-blockers; 3) diuretics; 4) angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists; 5) nitrates; 6) platelet aggregation inhibitors; 7) cholesterol-lowering drugs, i.e., 3-hydroxy-3-methylglutaryl coenzyme-A-reductase inhibitors (statins) or fibrates; 8) psychiatric medication, i.e., anti-depressants, antipsychotics and anxiolytics; 9) medication for Parkinson's disease or parkinsonism and 10) alpha-blockers.

Testing and data acquisition

The patients fasted overnight, and medication was withheld from midnight the night before. During testing, BP and heart rate were constantly measured using a Finometer (Finapres^{TM})(15) and a three-lead electrocardiogram. BP was measured at the non-dominant arm, which was held at heart level with a sling. The hydrostatic height correction system was used throughout the study to compensate for changing of the hand positions relative to heart level. The BP measurements were calibrated against brachial artery BP at baseline using the return to flow calibration system.(16,17) The raw data of BP and heart rate were stored in a data file. Unfortunately from 71 patients these raw data files could not be retrieved. This was a random selection, due to theft of the test laptop before back-up. Four patients were excluded because the BP measurements were not adequately determined, leaving 238 patients for analysis in the final sample. Data were exported using Beatscope^{TM} 1.1a software and analyzed with custom-written software in Matlab (version R2010b, The MathWorks Inc., Natick, Massachusetts, USA). After a 10-minute resting period in the supine position, the patients were instructed to stand up as quickly as possible, sometimes with

a helping hand, and remain standing for 10 minutes. Baseline values of BP and heart rate were defined as the average during the 20 seconds before standing up.

Hemodynamic response after active standing

For the first component of the hemodynamic response after standing we selected the decline of BP within the first 15 seconds. We determined the absolute maximum drop of SBP (ΔSBP) and the lowest SBP value that was reached in these first 15 seconds. The lowest SBP value (SBP min) was expressed as a percentage of baseline (pre-standing) SBP: $\%SBPmin = \frac{baseline\ SBP - \Delta SBP}{baseline\ SBP} x100\%$

For example if after standing up the SBP decreased from 120 mmHg to 90 mmHg this corresponds to a ΔSBP of 30 mmHg and a %SBPmin of 100 X (120 – 30)/120 = 75%. We did the same for DBP (ΔDBP and %DBPmin).

The second component of the hemodynamic response after active standing is the recovery of BP after the first 15 seconds. Therefore, the time between 15 to 60 seconds after standing was divided in nine time intervals of 5 seconds. For each time interval the average SBP and DBP was calculated as percentage of the baseline BP ($\%SBP_{15\text{-}20}$,$\%SBP_{20\text{-}25}$,....,$\%SBP_{55\text{-}60}$ and $\%DBP_{15\text{-}20}$,$\%DBP_{20\text{-}25}$,....,$\%DBP_{55\text{-}60}$). On the basis of the percentage SBP recovery at 55-60 seconds ($\%SBP_{55\text{-}60}$), we classified the patients into three groups with different recovery patterns in analogy to the earlier mentioned study of the association of SBP recovery patterns after standing with falls and frailty.(12) We used this time interval because after 60 seconds the period of interest for "classical" orthostatic hypotension starts. We defined patients with a full-recovery pattern to have recovery to >95% of their baseline SBP. The patients with a partial-recovery pattern had 80-95% and patients with a no-recovery pattern had <80% recovery.

All-cause mortality

The follow-up period ended on August 2010. Data on vital status were ascertained through linkages with the Dutch municipal administration. When the municipal administration could not provide this information, the general practitioner or the patient's family was contacted. For one patient, the exact date of death was not discovered, and another patient was lost to follow-up because of emigration. From these two patients, the year and month of death and emigration were known. For survival analysis, we used the month as the unit of time. Therefore, follow-up was complete for all patients.

Statistical analysis

Characteristics of the patients were compared with one way analysis of variance, or Kruskal-Wallis tests according to their recovery pattern. The results are presented as

the means ± standard deviations or percentages unless otherwise stated.

Cox proportional hazards models were used to identify whether ΔSBP, ΔDBP, %SBPmin and %DBPmin predicted mortality. The influence of the recovery of BP on mortality was studied with the same analyses on $\%SBP_{15\text{-}20}$ to $\%SBP_{55\text{-}60}$ and $\%DBP_{15\text{-}20}$ to $\%DBP_{55\text{-}60}$. Finally the same was done for the three recovery patterns. All above mentioned analyses were performed with two Cox proportional hazards models The first model was unadjusted. The second model was adjusted for age, gender, BMI, co-morbidity (CIRS-G score), and baseline SBP, DBP and heart rate. The results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).The results were considered to be significant for p-values<0.05. All analyses were performed using SPSS software version 16 for windows (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

The mean age of the 238 patients was 78.4±7.8 year and 64% was female. Examples of the three different recovery patterns are shown in Figure 1.

Table 1 describes the characteristics of the patients in the different recovery patterns. 95 patients (40%), 98 patients (41%) and 45 patients (19%) showed a full-, partial- or no-recovery response, respectively. Patients with no-recovery had a lower BMI than patients with a full- or partial-recovery (p<0.05). Patients with partial-recovery more often used calcium-channel-blockers than patients with full-recovery (p<0.05). Patients with no-recovery more often used anti-Parkinson medication than patients with a full-recovery (p<0.05).

Hemodynamic response after active standing

The mean overall change in SBP and DBP were 42±25 mmHg and 23±15 mmHg, respectively for the whole group of 238 patients. Table 2 gives the results for ΔSBP, %SBPmin, $\%SBP_{55\text{-}60}$ and ΔDBP, %DBPmin, $\%DBP_{55\text{-}60}$ respectively. The absolute initial drop of SBP and DBP did not differ between the three recovery groups, however as percentage of baseline %SBPmin and %DBPmin were slightly larger for the full-recovery response, compared to the partial- and no-recovery response. Figure 2 shows the mean relative SBP and DBP responses of the patients with the three different recovery patterns. In the initial 15 seconds, these patterns are more or less the same, however after 15 seconds the patterns become substantially different from each other.

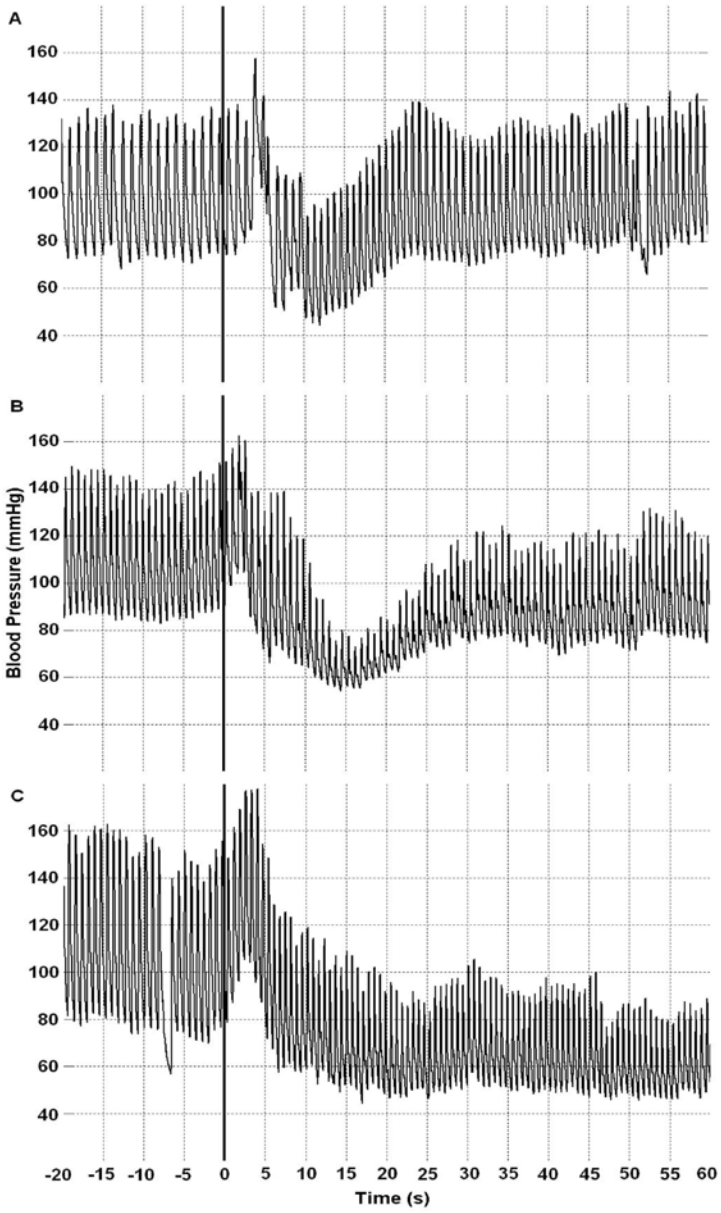

Figure 1 Examples of blood pressure recordings for three different blood pressure recovery patterns

A: full-recovery; B: partial-recovery; C: no-recovery. At time=0 seconds patients began to stand up after a verbal instruction.

All-cause mortality

During the median follow-up period of 21.0 months (range 1-61 months), 36 patients (15%) died. There were 8, 16, and 12 deaths in the 95, 98 and 45 patients with a full-, partial- or no-recovery response, respectively. There was no association between ΔSBP, ΔDBP, %SBPmin and %DBPmin and mortality in the unadjusted model (HR respectively: 1.01(95%CI 0.99-1.02); 1.00(95%CI 0.98-1.02); 0.99(95%CI 0.97-1.01) and 1.00(95%CI 0.98-1.01)).

During recovery of SBP after active standing, $\%SBP_{15\text{-}20}$, $\%SBP_{30\text{-}35}$ and $\%SBP_{40\text{-}45}$-$\%SBP_{55\text{-}60}$ were significantly associated with mortality, even after adjustment for age, gender, BMI, co-morbidity (CIRS-G score), baseline SBP, baseline DBP and baseline heart rate. The same was true for the recovery of DBP at $\%DBP_{25\text{-}30}$ and $\%DBP_{35\text{-}40}$-$\%DBP_{55\text{-}60}$, although after adjustment this was no longer significant for $\%DBP_{25\text{-}30}$ (Figure 3).The no-recovery group had a higher mortality risk than the full-recovery group (HR=2.94;95%CI 1.20-7.19). The partial-recovery group had an intermediate risk with a HR of 1.77 but this was not significant. The same pattern persisted after adjustment for baseline characteristics with HRs of 3.00(95%CI 1.17-7.68) and 1.95(95%CI 0.49-1.87) respectively for the no- and partial-recovery groups (Table 2). Since calcium-channel-blocker and anti-Parkinson medication use differed between the different recovery patterns (Table 1), we additionally adjusted for these, but this did not alter the results (Table 3). Figure 4 shows the adjusted Cox proportional hazards cumulative survival curves with respect to the three different recovery patterns.

Table 1 Comparison of the Baseline and Clinical Characteristics of the Patients with different blood pressure recovery patterns after change from supine to standing

Variable	Full-recovery (n=95)	Partial-recovery (n=98)	No-recovery (n=45)
Age	78.1±8.7	78.0±7.4	79.6±6.5
BMI	27.0±4.7	27.0±4.6	24.7±3.9†‡
Female, n(%)	55 (58%)	69 (70%)	29 (64%)
Baseline Systolic BP	167±25	167±28	170±33
Baseline Diastolic BP	78±12	83±21	79±10
Baseline heart rate	68±12	69±11	68±13
CIRS-G	11.1±4.6	11.1±4.5	10.8±4.4
Medical history			
Dementia	7 (7%)	5 (5%)	4 (9%)
Depression or anxiety	17 (18%)	18 (18%)	9 (20%)
COPD	15 (16%)	24 (25%)	5 (11%)
Diabetes mellitus	14 (15%)	18 (18%)	4 (9%)
Parkinson(ism)	2 (2%)	5 (5%)	4 (9%)
CVD	35 (37%)	40 (41%)	21 (47%)
Hypertension	43 (45%)	48 (49%)	23 (51%)
Malignancy	17 (18%)	17 (17%)	14 (31%)
Medication use			
Beta-blockers	32 (36%)	46 (47%)	32 (34%)
CCB	9 (10%)	22 (22%)*	7 (16%)
Diuretics	36 (38%)	36 (37%)	16 (36%)
ACE/AT2	32 (34%)	38 (39%)	17 (38%)
Nitrates	14 (15%)	13 (13%)	4 (9%)
PAI	38 (40%)	35 (36%)	19 (42%)
Statins/fibrates	31 (33%)	25 (26%)	9 (20%)
Psychiatric drugs	41 (43%)	30 (31%)	20 (44%)
Anti-Parkinson drugs	1 (1%)	2 (2%)	4 (9%)†
Alpha-blockers	4 (4%)	3 (3%)	4 (9%)

Results are reported as means ± standard deviations or numbers (percentages). Age(years); BMI, body mass index(kg/m^2); BP, blood pressure(mmHg); heart rate(beats per minute); CIRS-G, Cumulative Illness Rating Scale for Geriatrics; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CCB, calcium-channel-blockers; ACE/AT2, angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists; PAI, platelet aggregation inhibitors; *:significant differences ($p<0.05$) between patients with full-recovery and partial-recovery; †:significant differences ($p<0.05$) between patients with full-recovery and no-recovery; ‡:significant differences ($p<0.05$) between patients with partial-recovery and no-recovery.

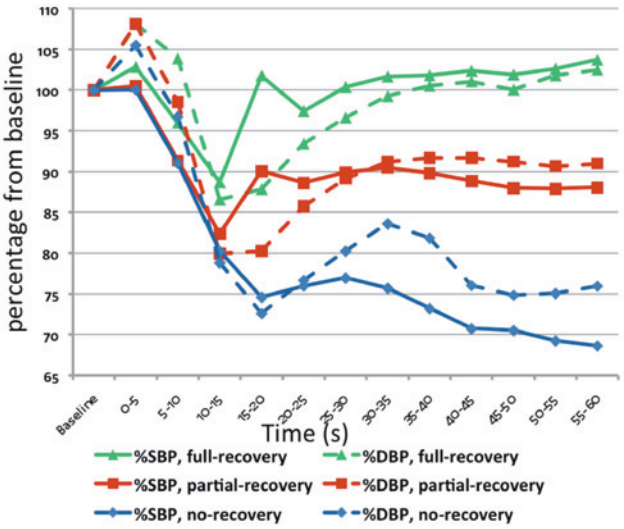

Figure 2 Mean blood pressure response in percentage from baseline upon active standing for the different systolic blood pressure recovery patterns

%SBP, percentage of the baseline systolic blood pressure; %DBP, percentage of the baseline diastolic blood pressure.

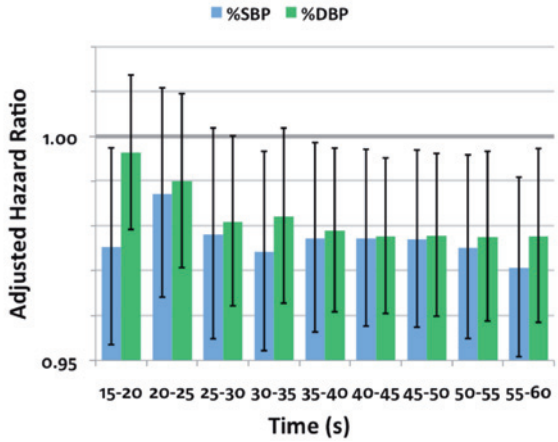

Figure 3 Cox proportional hazards ratios of %SBP and %DBP at different time intervals after active standing adjusted for age, gender, body mass index, co-morbidity, baseline SBP, baseline DBP and baseline heart rate

%SBP, percentage of the baseline systolic blood pressure; %DBP, percentage of the baseline diastolic blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2 Comparison of the results of the Patients with different blood pressure recovery patterns after change from supine to standing position

Variable	Full-recovery (n=95)	Partial-recovery (n=98)	No-recovery (n=45)
Systolic Blood Pressure			
ΔSBP (mmHg)	36±24	44±25	50±23
%SBPmin (%)	79±13	74±16*	70±24†
$\%SBP_{55\text{-}60}$ (%)	104±7	88±4*	69±12†‡
Diastolic Blood Pressure			
ΔDBP (mmHg)	19±12	27±19	25±12
%DBPmin (%)	76±15	68±16*	68±18†
$\%DBP_{55\text{-}60}$ (%)	102±11	91±12*	76±14†‡

Results are reported as means ± standard deviations. *:significant differences ($p<0.05$) between patients with full-recovery and partial-recovery; †:significant differences ($p<0.05$) between patients with full-recovery and no-recovery; ‡:significant differences ($p<0.05$) between patients with partial-recovery and no-recovery.

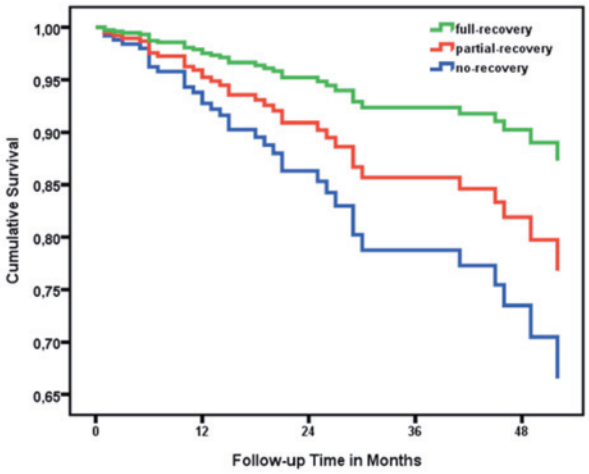

Figure 4 Cox proportional hazards cumulative survival curves with respect to different systolic blood pressure recovery patterns after active standing adjusted for age, gender, body mass index, co-morbidity, baseline SBP, baseline DBP and baseline heart rate

Full-recovery:>95% recovery of baseline SBP at 55-60 seconds; Partial-recovery:80-95% recovery of baseline SBP at 55-60 seconds; No-recovery:<80% recovery of baseline SBP at 55-60 seconds. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Cox proportional hazards analysis for all-cause mortality related to recovery pattern of systolic blood pressure after active standing

Recovery Pattern	Hazard ratio	95% Confidence interval	P-value
Full-recovery (>95%)	1	--	--
Partial-recovery (80-95%)	1.77	0.76-4.12	0.19
No-recovery (<80%)	2.94	1.20-7.19	0.02
Full-recovery (>95%)*	1	--	--
Partial-recovery (80-95%)*	1.95	0.49-1.87	0.14
No-recovery (<80%)*	3.00	1.17-7.68	0.02
Full-recovery (>95%)†	1	--	--
Partial-recovery (80-95%)†	2.20	0.90-5.40	0.09
No-recovery (<80%)†	3.09	1.21-7.89	0.02

*:adjusted for age, gender, body mass index, co-morbidity, baseline systolic blood pressure, baseline diastolic blood pressure and baseline heart rate.
†:adjusted as * and also for calcium-channel-blockers and anti-Parkinson medication use.

Discussion

The gravitational effects of standing up on cardiovascular hemodynamics lead to an initial fall in blood pressure that under normal conditions is restored to baseline within one minute. The main finding of this study is that impaired BP recovery in this first minute after standing predicts mortality, whereas the magnitude of BP decline within the first 15 seconds does not. The magnitude of the initial BP decline that follows standing up is a reflection of hydraulic mechanical properties of the vasculature (leg muscle pumping, abdominal compression, instantaneous vasodilatation)(3), whilst the subsequent recovery of BP reflects active functioning of the arterial baroreflex, the major mechanism involved in short-term BP regulation.(3)

The maximum SBP (42±25 mmHg) and DBP (23±15 mmHg) decline in our study was higher than in a previous study with 40 healthy subjects older than 70 years of age (26±23 mmHg and 12±18 mmHg, respectively).(18) This could be the result of involuntary Valsalva straining during standing up in our study, for which we did not explicitly control.(19,20). More likely, it is the result of studying different populations, i.e. very healthy and active elderly subjects versus elderly who visit a geriatric outpatient falls clinic. Our results were in line with a study in 442 community-dwelling elderly that reported a mean maximum SBP and DBP decline of 36 mmHg and 24 mmHg, respectively.(12)

We did not measure the exact time it took to assume the upright position, but it is known that elderly subjects need a longer time to stand up (3–9 s) than younger subjects (2–3 s).(21) This likely explains why the curves in Figure 2 are slightly shifted rightward compared to younger subjects.(8,22) Still, the curves are in line with the three different BP response patterns that have been recognized by cluster analysis.(12)

Our data add to the literature because for the first time to the authors' knowledge the impact on mortality of the immediate response of BP in the first minute upon active standing has been studied. There were no differences in co-morbidities and cardiovascular disease prevalence or hypertension between the three different recovery pattern groups. The observed higher mortality in the no-recovery group might therefore be a consequence of dysfunctional regulatory autonomic function, although hypotensive syndromes in geriatric patients are not explained by autonomic dysfunction alone.(23) The persistent BP decline and resulting hypoperfusion of organs might directly result in syncope, falls and even mortality. However, seen as a causal risk factor, not the amount, but the duration of the BP decline might be of more importance for mortality risk. This is in line with the observation that duration of SBP decline following active standing or sinus carotid massage is more important as a determinant of symptoms than SBP nadir or delta.(24,25)

However, a non-causal indirect relation of an impaired BP recovery (as a risk marker) with mortality is more likely. Active standing is a perturbation test, which elicits a more or less similar response in the initial BP decline in all subjects. However the regulatory capacity to normalize this perturbation largely differs between subjects. This failure to normalize BP is associated with excess mortality. In this context BP recovery in the first minute after active standing can be seen as a physical sign that reflects a final common pathway of various forms of subclinically impaired physiology.(26) Therefore, this BP recovery pattern fits in the search for easy, simple and non-invasive indicators of mortality in elderly people as for example gait speed or the (modified) physiologic index. (27-29)

For clinical application, the results of these two components of the BP response after standing (i.e drop and recovery) should be related to the well known syndrome of orthostatic hypotension. Orthostatic hypotension is defined as a drop in SBP of at least 20 mmHg, (30 mmHg in case of hypertension with resting SBP greater than 160 mmHg) and/or 10 mmHg in DBP often measured between 1 and 3 minutes after standing.(30) The percentage of patients with orthostatic hypotension increased from 18% (17/94) in the full-recovery patients to 55% (53/97) and 100% (45/45) in the partial- and no-recovery patients respectively. In our previous study there was no relation between orthostatic

hypotension and mortality after adjustment for confounders.(13) Therefore the recovery of SBP after 1 minute should be regarded as easily obtainable, additional information having better predictive value for mortality than the presence or absence of orthostatic hypotension.

Strengths and limitations

The present study has several strengths. Firstly, the follow-up in our study was complete. Secondly, the BP measurements in our study were performed under standardized circumstances, with a beat-to-beat finometer, which is an accurate way to measure BP variability.(31) Thirdly, co-morbidity was documented very thoroughly with the CIRS-G. The CIRS-G is frequently used in other studies, and good reliability and validity have been proven.(14,32) Fourthly, confounding effects of medication on the BP response were limited as much as possible. All medication was withheld from midnight the night before the test. Moreover there were no differences in medication use, except that patients with an impaired recovery (partial and no-recovery pattern) used more anti-Parkinson medication or calcium-channel-blockers. However, post-hoc correction for this medication use did not change the relation with mortality for these patients. Finally, we investigated a rather large group of 238 elderly patients on the relation of their response upon standing and mortality.

The present study has also some limitations. Firstly, this study was a retrospective analysis. The patients received a multifactorial falls intervention, which could have influenced mortality. However, a systematic review and meta-analysis showed no influence of multifactorial falls intervention on mortality among older people in community and emergency care settings.(33) Thus, although unlikely, we cannot completely rule out that our results may have been confounded by these multifactorial interventions. Secondly, we analyzed all-cause mortality but not cause-specific mortality, because it was impossible to reliably determine the cause of death. In older people, the cause of death is often unclear or related to multiple problems and thus, it is hard to validly assess without post-mortem data. Finally, this study investigated a selected patient population. All patients were referred because of syncope, falls and/or dizziness. This has the disadvantage of a specific selection and therefore our sample is not representative for the general population, but only for populations referred to similar outpatient clinics. On the other hand, this is the geriatric population with the highest relevance of BP dysregulation.

Conclusions

In falls clinic patients, failure to recover from BP decline in the first minute after active standing is associated with excess mortality. Therefore, SBP recovery to less than 80% from baseline after 60 seconds may be used as an easy available cardiovascular sign for increased mortality risk in older falls clinic patients.

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Chapter 5a

Baroreflex function is reduced in Alzheimer's disease: a candidate biomarker?

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5

Abstract

Background

The baroreflex (BR) reflects autonomic blood pressure control. Alzheimer's disease (AD) affects the autonomic system. Detailed properties of BR in AD are unknown. We hypothesized that BR is reduced in AD, and is influenced by autonomic effects of cholinesterase inhibitors (ChEI).

Methods

BR was determined in 18 AD patients, 11 patients with mild cognitive impairment (MCI) and 19 healthy control subjects. In AD, BR was measured again after ChEI treatment. Receiver operating characteristic (ROC) analysis was used to define a BR cut-off value, which was then tested in an independent validation sample of 16 AD, 18 MCI and 18 control subjects.

Results

BR was lower in AD compared to MCI ($p<0.05$) and in MCI compared to healthy control subjects ($p<0.01$). ROC analysis between AD and healthy control subjects yielded a sensitivity of 89% and a specificity of 94%. ChEI treatment increased BR with 66% ($p<0.01$).

Conclusions

BR was reduced in AD and increased after treatment with ChEI. BR may be a good biomarker to further explore the link between cardiovascular disease and AD.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is the leading cause of dementia. Worldwide, AD is among the top 5 of most costly diseases and places a huge burden on individual caregivers.(1) There is still a limited understanding of this disease and its underlying cause, which is reflected in the lack of an effective curative treatment for AD.

Many of the currently developed and tested therapies are based on the amyloid cascade hypothesis. This hypothesis, supported by convincing genetic data, proposes that the extensive neuronal damage in AD is caused by increased concentration and aggregation of β-amyloid.(2) However, this theory does not offer an explanation for how this process is initiated in sporadic forms of AD, nor for the observation that the earliest changes in AD do not include amyloid deposition.3 Criticism regarding the amyloid hypothesis has fueled the popularity of the vascular hypothesis for AD, which states that cardiovascular disease is an important causal or contributing factor in sporadic AD.(4-7)

Although cardiovascular factors are now commonly accepted as risk factors for AD, the exact relationship between these factors and AD remains poorly understood. For example mid-life hypertension increases AD risk and anti-hypertensive treatment potentially reduces this risk(8,9), suggesting a unidirectional, possibly causal relationship between hypertension and AD. However, subjects with a parental history of sporadic AD are more likely to have hypertension than control subjects(10), suggesting either a causal relationship between AD and hypertension or a shared causative factor. Moreover, blood pressure (BP) levels decline from hypertension to normotension or even to hypotension during the course of AD.(11) These data imply a relationship wherein AD may influence BP or BP may influence AD. Better understanding of the relationship between BP control and AD may therefore provide important new clues towards our understanding, and ultimately, treatment, of AD.

A possible link between AD and BP is the baroreflex (BR). The BR is a reflex loop with cardiac, vascular, and cerebral components involved in short-term BP regulation.(12) The BR operates via the autonomic nervous system to restore sudden changes in BP by changing heart rate (HR) or vascular tone. A clinical example is the drop in BP upon standing, which the BR corrects by a rapid increase in HR (parasympathetic inhibition) followed by peripheral arterial vasoconstriction (sympathetic activation). The cholinergic system is an important component of cardiovascular and autonomic control, including the BR. This cholinergic system is prominently affected early in AD.(13,14) Therefore, we hypothesized that BR function is reduced early in patients with AD.(15)

In this study, we further explored this hypothesis in three steps. First, we compared BR function between patients with AD, patients with Mild Cognitive Impairment (MCI) and healthy elderly subjects. Patients with MCI are thought to represent patients with very early-stage AD. The second step was to validate our findings in an independent sample of AD patients, MCI patients and elderly control subjects. The third and final step was to explore the role of the cholinergic deficit on BR function in AD, by testing the influence of cholinesterase inhibitors on BR function in a subgroup of patients with AD.

Methods

Study population

Overall, this study included 34 patients with mild to moderate AD, 29 patients with MCI and 37 healthy control subjects in two distinct samples: (1) a derivation sample: 18 patients with AD (72 ± 6 years), 11 patients with MCI (71 ± 9 years), and 19 healthy control subjects (75 ± 3 years), recruited at Radboud University Nijmegen Medical Centre (RUNMC), and (2) a validation sample: 16 AD patients (71 ± 8 years), 18 patients with MCI (70 ± 7 years), and 18 healthy control subjects (70 ± 6 years) recruited at Maastricht University Medical Center (MUMC). Data on cerebral hemodynamics from the RUNMC AD patients and control subjects and from the MUMC AD and MCI patients and control subjects have been published recently.(16,17)

In both samples, recordings of electrocardiograms (ECG) and beat-to-beat photoplethysmographic BP were obtained. There was a difference in body position during measurements between the two samples. Subjects at RUNMC were seated while ECG and BP were recorded, whereas the subjects at MUMC were supine.

All subjects from both centers were examined by a geriatrician, and carefully screened to exclude acute medical conditions. A subset of subjects (15 control subjects; 15 MCI patients; 29 AD patients) had an MRI scan of the brain to investigate medial temporal lobe atrophy (MTA). Informed consent was obtained from all patients and healthy control subjects before they entered the study. Both studies were approved by the medical ethical committees of the corresponding centers.

Patients with MCI and AD were diagnosed by a multidisciplinary memory clinic team using the NINCDS-ADRDA criteria(18,19) and MCI consensus criteria(20) based on clinical evaluation and additional diagnostic tests if indicated, such as MRI-scan of the brain, neuropsychological testing, and cerebrospinal fluid analysis. In the derivation sample from RUNMC, BR in AD

patients was measured before and after 8 weeks of treatment with a cholinesterase inhibitor (galantamine, 4 weeks of 8 mg followed by 4 weeks of 16 mg). In the validation sample from MUMC, 10 of the 16 AD patients were already treated with cholinesterase inhibitors when BR was measured.

Data acquisition and pre-processing

The ECG was recorded using a three-lead system and beat-to-beat HR was obtained from each R-R interval identified from the QRS complexes. Arterial BP was measured noninvasively at the middle finger of the right hand using Finapres (Finapres Medical Systems) at RUNMC and the Task Force Monitor (CN Systems) at MUMC, respectively. It has been shown that BP measured on the finger by photoplethysmography is similar to conventional auscultatory measurements on the upper arm.(21) For both systems, the finger pressure cuff was positioned carefully at heart level with the hand being held in the left midaxillary line. The hand and arm were supported securely and comfortably with a sling. The subjects underwent several minutes of customization and the servo-adjust mechanism was turned off prior to recording. Periods of 100 s of artifact- and calibration-free data were selected by visual inspection of the time series of the tachogram and systogram and used for subsequent analysis. The time series were linearly interpolated at 1 Hz to obtain equidistant time intervals. The time series were detrended and filtered with an eighth-order high-pass Butterworth filter (0.02 Hz), to ascertain signal stationarity.

Causal model BR estimation

Baroreflex sensitivity (BRS) is often evaluated noninvasively by assessing heart-rate variability (HRV) and systolic blood pressure (SBP) variability. However, studies using HRV and SBP variability often report contradictory results.(22-24) A possible explanation for this inconsistency is that the estimation of the baroreflex by means of HRV assumes but not tests that the whole R-R interval variability is generated by SBP changes. Therefore the causal dependencies are not taken into account. In this study, a bivariate causal model (ARXAR model), which was first introduced by Nollo et al. in 2001, was used to quantify the BR. With this model it is possible to describe the causal relationship from SBP to R-R interval (the baroreflex pathway) and to separate it from the mechanical pathway (from RRi to SBP). Details of this method are described elsewhere.(25)

In short, the interactions between R-R interval and systolic blood pressure (SBP) are modeled as follows:

$$RR(n) = -\sum_{k=1}^{p} a_k RR(n-k) + \sum_{k=1}^{p} b_k SBP(n-k) + u(n)$$

According to the ARXAR model, the RR series is affected by p samples of its own past (by a_k coefficients) and by p samples of the SBP sequence (by b_k coefficients). The effects of other sources independent from SBP on R-R interval variability, considered as noise in this context, are accounted for in the model by means of the u(n). As outlined in Figure 1, the SBP and u signals are described as autoregressive processes with wsbp and wrri zero-mean input white noises.

The blocks C and D are formed by the autoregressive parameters of SBP and u, respectively. In the open loop ARXAR model the variability of SBP around its mean value is considered as an exogenous input, i.e. it may affect the R-R interval variability without itself being affected by the R-R interval variability. The coefficient estimation follows an iterative identification task based on the generalized least squares method. The model order p was chosen minimizing the Akaike figure of merit for the bivariate joint process |RRi SBP|.(25) The gain of the R-R interval – SBP transfer function (G(f)) was estimated directly from the coefficients of the A and B blocks. The value of the gain in the low frequency (LF) band (0.04 – 0.15 Hz) was considered by sampling G(f) on the LF peak of the spectrum of the driving SBP series.(26) It has been shown that there is a good agreement of the causal model with the traditional phenylephrine test to determine baroreceptor responsiveness.(25)

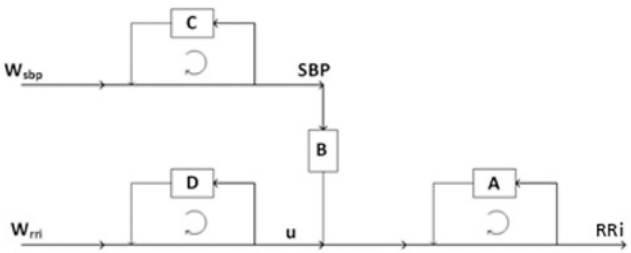

Figure 1 Bivariate autoregressive model with exogenous input (ARXAR model) for the description of the causal effects of SBP on R-R interval. In the open loop scheme, RRi values are separately determined by the exogenous input sbp and by sbp-unrelated variations described by the series u (Nollo, et al., 2001).

Statistics

Results are presented as the mean ± standard deviation (SD) or percentage, unless stated otherwise. Differences in baseline variables and BR between control subjects and patients were evaluated with the Mann-Whitney test for continuous variables and chi-squared (χ^2) statistics for proportions. Sensitivity and specificity pairs for different BR values distinguishing the groups were determined. These sensitivity and specificity values were used to construct a receiver operating characteristic (ROC) curve, in which the optimal sensitivity and specificity combination is visualized. A p-value < 0.05 was considered statistically significant.

Results

Derivation sample

Sample description

Eighteen AD patients (11 women), 19 age-matched healthy control subjects (5 women), and 11 MCI patients (6 women) from RUNMC participated in this study and had the BR measured successfully. Table 1 summarizes the sample characteristics. AD and control subjects did not differ with respect to SBP. However, SBP in MCI patients was higher than in the healthy control subjects ($p<0.01$).

Baroreflex function

BR function was calculated in correspondence with the peak in the power spectra of the SBP between 0.04 and 0.15 Hz (dashed line), the frequency range in which BR modulation of HR occurs.

Mean values of the BR gain obtained by the ARXAR model are shown in Figure 2. BR was lower in AD (1.4 ± 0.8 ms/mmHg) compared to control subjects (6.4 ± 2.7 ms/mmHg) ($p<0.01$). BR in MCI (2.9 ± 0.7 ms/mmHg) differed from both AD ($p<0.01$) and control subjects ($p<0.01$) and was in between the values for AD and control subjects. The area under the ROC curve for the relationship between AD and healthy elderly was 0.92 (Figure 3). With a threshold (cut-off point) of 3.2 ms/mmHg for AD, sensitivity was 89% and specificity was 94%.

Validation sample

Sample description

SBP and R-R interval data were obtained from 16 AD patients (9 women), 18 age-matched healthy control subjects (9 women) and 18 MCI patients (10 women) from MUMC. Table 1 summarizes their characteristics. In the derivation sample

Table 1 Characteristics of derivation and validation sample

	Derivation sample			Validation sample		
	Control	MCI	AD	Control	MCI	AD
	(n = 19)	(n = 11)	(n = 18)	(n = 18)	(n = 18)	(n = 16)
Age (years) [mean ± SD]	75 ± 3	74 ± 9	72 ± 6	70 ± 6	70 ± 7	71 ± 8
Sex (male/female)	14 / 5	5/6	7 / 11	9 / 9	8 / 10	7 / 9
MMSE (0-30) [mean± SD]	29 ± 5	25 ± 3*	22 ± 5*	29 ± 1	28 ± 1†	21 ± 4*
MTA [mean]	0.6		2*			
Hypertension (n(%))	4 (27)	7 (64)*	6 (33)	9 (50) †	6 (55)	7 (44)
HR (bpm) [mean± SD]	62 ± 8	60 ± 12	71 ± 12	58± 6†	60 ± 8	62 ± 7
SBP(mmHg) [mean ± SD]	125 ± 20	152 ± 25*	133 ± 31	136 ± 16	133 ± 17†	133 ± 15
Medication use						
- Beta blocker	2 / 19	4 / 11	5 / 18	0 / 18	3 / 18	0 / 18
- ACE inhibitor	0 / 19	0 / 11	3 / 18	0 / 18	0 / 18	0 / 16
- ARB	0 / 19	0 / 11	1 / 18	0 / 18	0 / 18	0 / 16
- Calcium channel blocker	0 / 19	1 / 11	2 / 18	0 / 18	0 / 18	0 / 16
- Thiazide diuretics	3 / 19	0 / 11	4 / 18	0 / 18	1 / 18	0 / 16
- Vasodilator	0 / 19	1 / 11	1 / 18	0 / 18	0 / 18	0 / 16

The results are reported as mean ± standard deviation, absolute number or frequencies. MMSE, Mini Mental State Examination; MTA, medial temporal lobe atrophy; HR, heart rate; SBP, systolic blood pressure; ACE inhibitor, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker. * significantly different ($p<0.05$) from the control group of the same sample. † significantly different from the matching group of the derivation sample.

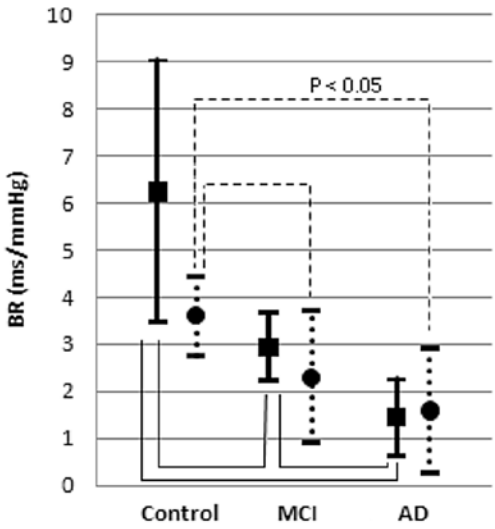

Figure 2 BR values in mean ± standard deviation for the three groups (MCI patients, patients with AD and healthy age-matched control subjects)

The solid lines represent the derivation sample and the dashed lines represent the validation sample. Significant differences are indicated by the connecting lines (dashed for data of the derivation sample, and solid for data of the validation sample).

(RUNMC), MCI patients had higher SBP than healthy control subjects. This was not the case in the validation sample from MUMC. There were additional differences between the derivation and validation sample: the MUMC MCI group had lower SBP (133 mmHg) than the RUNMC MCI group (152 mmHg) (p=0.02) and the MUMC control group had a lower HR (58 bpm) compared to the RUNMC control group (62 bpm) (p=0.04).

Baroreflex function

BR function was calculated in the same way as for the derivation sample. Mean values for BR gain obtained by the ARXAR model are shown in Figure 2 (dashed lines). Also here, BR was lower in AD (1.6 ± 1.3 ms/mmHg) compared to healthy control subjects (3.6 ± 0.8 ms/mmHg) (p<0.01). BR gain in the MCI group (2.3 ± 1.4 ms/mmHg) also was lower than in healthy control subjects (p<0.01), and higher than AD (p=0.03). Application of the BR cut-off value of 3.2 ms/mmHg, as it had been obtained in the derivation sample, yielded a sensitivity of 93 % and a specificity of 78 % for differentiating AD from healthy control subjects in this validation dataset (Table 2).

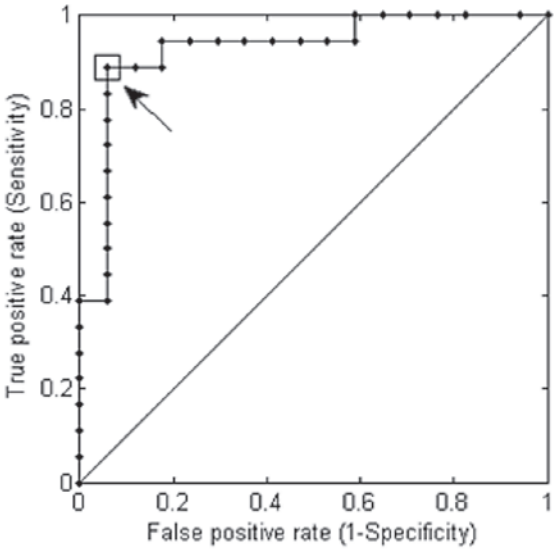

Figure 3 ROC curve analysis of the predictive value of BR in distinguishing AD patients from healthy control subjects

The area under the curve equals 0.92; 95% confidence interval is 0.84-1.00; p-value < 0.01. The square shows the optimal BR cut-off point at 3.2 ms/mmHg resulting in a sensitivity of 89% and a specificity of 94% is reached.

Table 2 Performance of the proposed baroreflex cut-off score

Baroreflex value	n of patients (% of total)	AD	Control	sensitivity	specificity
≤ 3,2 ms/mmHg	18 (51 %)	14	4	93%	78%
> 3,2 ms/mmHg	17 (49 %)	1	14		

Performance of the proposed baroreflex cut-off score to distinguish between AD and healthy control subjects, in the validation sample.

Cholinesterase inhibitors

In eighteen AD patients (11 women) in the derivation sample, SBP and R-R interval data were obtained before and after treatment with cholinesterase inhibitors. Following treatment with cholinesterase inhibitors, BR increased from 1.4 ± 0.8 ms/mmHg to 2.4 ± 0.9 ms/mmHg ($p<0.01$). In the validation

sample, no before-after cholinesterase-inhibitor treatment comparisons were available, however in this sample, BR was higher in the 10 patients who were treated with cholinesterase inhibitors (2.0 ± 1.5 ms/mmHg) compared with the 6 patients without. (0.89 ± 0.4 ms/mmHg) (p=0.02). Cholinesterase-inhibitor-treated patients in the derivation sample had a slightly higher BR than those in the validation sample (p=0.03).

Discussion

The main finding of our study is that the BR function is lowered in patients with AD compared to age-matched control subjects. Our results are in agreement with the depressed BR sensitivity observed in 24 patients with AD.(27) Our study adds to these observations by the addition of a group of patients with MCI, reflecting early-stage AD, by reproducing our findings in an independent sample, and by investigating the effect of cholinesterase inhibitors on BR. Furthermore, a more precise BR quantification method was used. The traditional sequence analysis used in the study of Szili-Török et al.(27) assumes, but not tests, that the whole R-R interval variability is generated by SBP changes. The method used in our study takes this causal dependency into account by dividing the R-R interval variability in SBP-related and SBP-unrelated parts.

The difference in BR function was so prominent that it was possible to distinguish patients with AD from control subjects by their BR function. The discriminatory value of BR was so strong that it achieved a performance that compares with or even exceeds that of current diagnostic biomarkers, such as cerebrospinal fluid analysis of amyloid β42. Indeed, a cut-off value for BR gain of 3.2 ms/mmHg reached a sensitivity of 89% and a specificity of 94% to discriminate AD from control subjects in the derivation sample. For comparison, cerebrospinal fluid analysis of amyloid β42 has an ROC of 0.9, with a sensitivity of 93% and a specificity of 87% to discriminate AD from control subjects.(28) This discrimatory cut-off value for BR performed equally well in the independent validation sample with a sensitivity of 93% and a specificity of 78% for differentiating AD from healthy control subjects. Additionally, MCI patients had a BR value that was intermediate between control subjects and AD. A strength of our study is that also these results were confirmed in the independent validation sample.

These findings underscore the importance to explore the underlying mechanism that explains this association between impaired BR functioning and AD. They raise the question whether AD pathology results in impaired BR functioning or whether impaired BR functioning contributes to (acceleration of) AD pathology.

Possible mechanism and consequence of the decreased BR in AD

The BR is the major feedback control system for BP. Primary afferent fibres from arterial baroreceptors - in the carotid sinus and aortic arch - send information to the nucleus tractus solitarius in the medulla oblongata.(29) From here, information is sent via interneurons to the hypothalamus or to higher regions in the brainstem and forebrain(30), including the insular cortex.(31) The insular cortex is a recognized site of autonomic cardiovascular control and baroreflex-mediated autonomic cardiovascular function.(32) In 1998, Braak et al.(33) demonstrated a hierarchical progression of AD pathology that includes the insular cortex in an early stage. This insular involvement may lead to changes in cardiovascular and autonomic control, and may consequently affect the BR.(32,34)

Further circumstantial evidence is found in the effects of exercise. Exercise improves cardiovascular function and BR.(35) Exercise has also been shown to lower the risk of AD.(36) Although direct associations between exercise, BR and AD risk have not been investigated, and BR could be no more than a marker of exercise, it can be hypothesized that BR function is part of the causal pathway that links exercise to reduced AD risk, or that augmented BR is a marker of beneficial effects of exercise on autonomic brain centers.

Here, we have also shown that treatment with cholinesterase inhibitors augmented BR function in AD. This is in line with recent findings that atropine, in a dose which augments vagal tone, increased cardiovagal baroreflex gain in older subjects.(37) Our findings cannot be explained by age-related effects only(38) because we compared AD and MCI patients with age-matched healthy control subjects. Cholinesterase inhibitors partly compensate for the cholinergic deficit in AD. The cholinergic system has a pivotal role in learning and memory.(39) However, the augmented BR function suggests that cholinesterase inhibitors may slow clinical disease progression not only through direct cognitive effects but also through their influence on cardiovascular factors such as BP regulation. Our findings may extend to preclinical and early clinical AD, for example patients with MCI. Patients with MCI have a high risk of progression to dementia, particularly of the Alzheimer type.(20,40) There is a greater orthostatic fall in SBP in MCI and Alzheimer patients than in control subjects(22,23) and the prevalence of orthostatic hypotension in MCI patients lies between control subjects and AD patients.(41) This observation parallels the BR values in control subjects, MCI and AD found in our study and is in line with an earlier study which showed an association between blunted baroreflex functioning and increased risk of orthostatic hypotension.(42)

Despite the fact that several studies have shown an association between AD and autonomic instability, such as increased pupillary dilatation(43), diminished

HR variability(44), and orthostasis, the significance of the abnormalities in BR among AD patients is not yet fully known. However, impaired BR in other common dementia subtypes, such as Parkinson's disease and Lewy Body Disease, is held partly responsible for the higher prevalence of orthostatic hypotension(22) and increased cardiovascular mortality. These patients also exhibit a significant loss of cholinergic forebrain neurons.(45)

BR functioning as diagnostic tool

In the perspective of new therapeutic options to slow the progression of dementia, an early diagnosis of AD is of utmost importance because all treatment strategies are more effective in the earlier phases of the disease.(46) In this study, a rapid, noninvasive, and inexpensive procedure without need for active patient cooperation was used to estimate BR function from ECG and BP recordings, obtained when the patient quietly sits or lies down. Our results show that in patients with AD, a lowered BR could be a sensitive and specific marker of the disease. A strength of the study is the consistent decrease in BR found over the different groups (from healthy subjects to MCI patients to AD patients). This result points towards a disease-specific involvement of the BR. However, although we have shown that BR discriminates between AD and control subjects, further evidence must be obtained for its discriminatory value against important differential diagnoses in memory clinics, i.e. other causes of dementia and depression.

Limitations

Some methodological issues need to be considered. First of all, the diagnosis of AD and MCI in our study remains a clinical one. There was no pathological confirmation of the underlying disease. However, previous studies have shown that a clinical diagnosis is only inaccurate, compared to pathological diagnosis, in about 11% of mild cases.(47) The patients with MCI and AD were diagnosed by a multidisciplinary memory clinic team consisting of several geriatricians, neuropsychologists, occupational therapists and speech therapists. Lewy body dementia and vascular dementia were excluded based on diagnostic criteria for these conditions, using information obtained by means of history, clinical examination, laboratory tests and additional, mostly radiological, investigations. In a population referred to a memory clinic (as in this study), depending on criteria, a high percentage of MCI patients will develop AD.(48,49) Still, in some patients MCI remains stable and never progresses to AD. Therefore the assumption that abnormal BR function serves as early detection of the Alzheimer disease process remains hypothetical. To overcome this limitation, larger scale studies with follow-up of MCI and AD patients are needed, with observations of

BR during the different stages of progression of AD. Maybe a combination with other easy to determine parameters, in particular the cerebrovascular resistance index(16), could enhance discrimination of patients at risk for developing AD.

Secondly, it may be argued that results should have been corrected for differences in use of medication, since we included patients with co morbidities and medication. There is some information about whether commonly used anti-hypertensives, such as metoprolol and enalapril, can augment the cardiac autonomic function in hypertensive patients. Keeley et al. showed that beta-blockers can directly improve cardiovascular autonomic regulation in normotensive and hypertensive patients.(50) Further, Mancia et al. showed an increase in BR function when the circulating levels of angiotensin II and aldosterone were reduced by angiotensin-converting enzyme (ACE) inhibitors. (51) Because antihypertensive drugs mostly show an increase of the BR function, we argue that the difference in BR function between AD patients and healthy elderly would have been even greater when the AD patients had used no antihypertensives.

Thirdly, some differences exist in population and protocol characteristics between the derivation and validation sample. In the validation sample the control subjects had a higher SBP (136 mmHg compared to 125 mmHg) than in the derivation sample. Furthermore, in the derivation sample BP and HR were obtained in the sitting position, in the validation sample BP and HR were obtained supine. These differences may explain the difference in BR between the two control groups (6.4 ms/mmHg in the derivation sample versus 3.6 ms/mmHg in the validation sample). Bristow et al. showed an inverse relationship between resting mean BP and BR, with reduced BR sensitivity in hypertension. (52) This might explain the observed lower BR in the derivation sample where the SBP was higher. However, literature yields discordant results about the influence of posture on the BR results.(53,54)

Finally, a limitation of the study is the cross sectional design. This design allows us to establish the relationship between BR and AD, but we are unable to establish whether the impaired functioning of the BR is the effect or the cause of neurodegeneration.

Conclusions

This study shows a strong association between AD and diminished BR function. A possible link is the cholinergic system which is involved in both BR and AD. Cholinesterase inhibitors increase BR function in AD. Furthermore, MCI patients have an intermediate BR function between the normal and the AD subjects.

Considering this, it is possible that early in AD besides cognition also BP regulation is affected. Further research on the relationship between BR and AD might provide valuable insights into the pathophysiology and for the diagnosis and treatment of AD.

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5

Chapter 5b

Average daily blood pressure is associated with progression of cerebrovascular disease and cognitive decline in older people. What is the influence of blood pressure variability?

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5

To the Editor: With interest we have read the article by White et al.(1) In their well-designed prospective cohort study, they demonstrate the importance of increased 24-hour systolic blood pressure, but not clinic systolic blood pressure, in the progression of brain white matter hyperintensity volume burden associated with impairment of cognitive function in older people. They conclude that 24-hour of systolic blood pressure may be a potential target for intervention in the elderly to reduce vascular disease of the brain and impairment of function. Unfortunately, they did not take blood pressure variability into account , and they did not measure small-vessel disease more precisely with diffusion tensor-imaging measures. Visit-to-visit variability in systolic blood pressure is a strong predictor of stroke, independent of mean systolic blood pressure.(2) Even in patients with treated hypertension, an increased residual variability in systolic blood pressure is associated with a high risk of vascular events.(2) However, stroke has a different pathophysiology compared to small-vessel disease that is reflected in white matter intensity lesions. Moreover, visit-to-visit blood pressure variability does not reflect the same regulatory mechanisms as regular blood pressure measurement with a 24-hour ambulatory blood pressure monitoring device. Nevertheless, in a small sample of 39 older adults with cardiovascular disease, in whom blood pressure was measured using an automated monitor every 10 minutes for 2 hours, systolic blood pressure variability was associated with white matter hyperintensities.(3) Therefore, blood pressure variability, but also blood pressure instability (like orthostatic hypotension), might provide additional information on the association between blood pressure and the presence of small-vessel disease.

Next, small-vessel disease was only measured by conventional magnetic resonance imaging measurement of white matter hyperintensity volume. Diffusion tension imaging has been shown to be of added value in explaining cognitive function based on brain imaging.(4) This is explained by the fact that small-vessel disease is already causing microstructural damage in the white matter, even on strategic places, which can be measured by diffusion tension imaging but are still missed by focusing on white matter hyperintensities.

In conclusion, White et al.(1) provide convincing evidence for the association between 24-hour systolic blood pressure and white matter hyperintensities. However, when blood pressure variability is added to the usual static systolic blood pressure in their analysis, it might potentially further refine and optimize the target for intervention in the elderly to reduce vascular disease of the brain and impairment of function.(5) Therapeutic effects of blood pressure treatment probably are best followed by serial diffusion tension imaging measurements, as diffusion tension imaging measures are a better reflection of early changes in small-vessel disease in the brain.

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Chapter 6

Oscillations in cerebral blood flow and cortical oxygenation in Alzheimer's disease

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Abstract

In Alzheimer's Disease (AD) cerebrovascular function is at risk. Transcranial In Alzheimer's Disease (AD) cerebrovascular function is at risk. Transcranial Doppler, near-infrared spectroscopy, and photoplethysmography are non-invasive methods to continuously measure changes in cerebral blood flow velocity (CBFV), cerebral cortical oxygenated haemoglobin (O_2Hb), and blood pressure (BP). In 21 patients with mild to moderate AD and 20 age-matched controls, we investigated how oscillations in CBFV and O_2Hb are associated with spontaneous and induced oscillations in BP at the very low (VLF = 0.05 Hz) and low frequencies (LF = 0.1 Hz). We applied spectral and transfer function analysis to quantify dynamic cerebral autoregulation and brain tissue oxygenation. In AD, cerebrovascular resistance was substantially higher (34 %, AD vs. control: Δ = 0.69 (0.25) mmHg/cm/s, p = 0.012) and the transmission of VLF cerebral blood flow (CBF) oscillations into O_2Hb differed, with increased phase lag and gain (Δ phase 0.32 (0.15) rad; Δ gain 0.049 (0.014) μmol/cm/s, p both < 0.05). The altered transfer of CBF to cortical oxygenation in AD indicates that properties of the cerebral microvasculature are changed in this disease.

Introduction

In patients with Alzheimer's disease (AD) and in mouse models of AD, the structural integrity of the cerebral vasculature, especially of cortical microvessels, is markedly compromised.(1) Additionally, dynamic cerebral autoregulation, the vascular mechanism which aims to stabilize brain perfusion, is impaired in mouse models of AD.(2,3) Whether dynamic cerebral autoregulation is also altered in human AD remains unknown. Recently, we have shown that patients with early stage AD have a reduced cerebral blood flow velocity (CBFV) and an increased cerebrovascular resistance (CVR) compared to age-matched healthy controls. Moreover, AD patients had smaller spontaneous cerebral blood flow (CBF) oscillations, relative to blood pressure (BP) oscillations. This implies a reduction in transfer function gain, a parameter that quantifies dynamic cerebral autoregulation and describes how changes in BP are transferred to changes in CBFV.(4) Notably, changes in CBFV were measured using transcranial Doppler (TCD) in the middle cerebral artery (MCA), reflecting global changes in cerebral blood flow (CBF) but not necessarily changes that occur at brain tissue level.(5)

Near-infrared spectroscopy (NIRS) and functional MRI have revealed spontaneous oscillatory changes in cerebral cortical oxygenation.(6) These oscillations appear similar to those observed in CBFV and BP.(7) However, the exact characteristics of the relationship between dynamic changes in CBFV measured in the basal cerebral arteries and brain tissue oxygenation remains unknown. It is possible that oscillations in brain tissue oxygenation are induced by changes in global CBF and that the dynamic relationship between these variables reflects not only the function of the cerebral vasculature to deliver oxygen to the brain tissue, but also brain tissue oxidative metabolism.(8) We hypothesized that the presence of vascular abnormalities in AD may alter this dynamic relationship between CBF and brain tissue oxygenation. In this article we focus on the two different but dependent dynamic relationships, the relation between BP and CBF on the one hand and the relation between CBF and cerebral cortical oxygenation on the other.

Cerebral blood flow velocity in the middle cerebral artery changes dramatically if large changes in BP are induced by changes in body posture from sitting or squatting to upright standing.(9,10) This provides a model to study not only the relationship between BP and CBF, but also between CBF and cerebral cortical oxygenation. The aim of this study was to test the hypothesis that oscillations in BP and CBF, associated with changes in body posture, are transmitted into changes in brain cortical oxygenation and that this dynamic relationship is altered in patients with mild to moderate AD.

For this purpose, beat-to-beat changes in BP, CBFV, and concentrations of frontal cortical oxyheamoglobin (O_2Hb)] and deoxy-heamoglobin (HHb) were

measured continuously using finger arterial BP measurements, TCD and NIRS, during repeated sit-stand maneuvers in patients with newly diagnosed AD. Fourier spectral and transfer function analysis were used to quantify the magnitude of oscillations and the dynamic relations between these variables. The repeated sit-stand maneuvers were performed to augment the spontaneous BP and CBFV oscillations.(10) They induce large oscillations in BP, CBFV, and O_2Hb and enhance the coherence between these variables (> 0.4) and therefore improve the reliability of the transfer function analysis.(5) The repeated sit-stand maneuvers were performed at 0.05 and 0.1 Hz. At the very low frequency (0.05 Hz) dynamic cerebral autoregulation is active, but in the low frequency (0.1 Hz) dynamic cerebral autoregulation is less active.(11)

Methods

Subjects

We recruited 21 AD patients, aged 65 years and older. All patients had been newly diagnosed with AD in the memory clinic at Radboud University Nijmegen Medical Centre. Patients were diagnosed with mild or moderate AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), Clinical Dementia Rating (CDR) 0.5 – 2.(12) They were not yet treated with cholinesterase inhibitors. As a control group, 20 age-matched healthy old persons were selected from a group of volunteers that responded to a newspaper advertisement. All patients and volunteers were carefully examined by a geriatrician, including physical examination, laboratory evaluation, CT (n = 2) or MRI-scan (n =39) of the brain, and neuropsychological testing. All controls and randomly selected patients (n = 10), underwent a Doppler study of the carotid and vertebral arteries to rule out significant stenosis (> 50 %).

The study was approved by the Ethics Committee for Research on Human Subjects, Radboud University Nijmegen Medical Centre, and all volunteers and primary caregivers of the AD patients gave written informed consent, and AD patients themselves gave verbal consent.

CBFV and NIRS measurements

Using TCD, CBFV was measured in the MCA. Changes in CBFV represent changes in flow, under the assumption that the diameter of the insonated vessel remains constant. The MCA is one of the major conduit arteries of the cerebral circulation and branches directly from the common carotid artery. Many studies

have demonstrated that the diameter of the MCA does not change appreciably even during moderate alterations in BP and end-tidal CO2.(13-15) Therefore, changes in CBFV should represent predominately changes in CBF in this study. Further it was assumed that there is no displacement of the MCA with respect to the probe position during repetitive vertical postural changes.(9)

NIRS measures cerebral cortical changes in O_2Hb and HHb. The basic principle of NIRS is that near-infrared light penetrates the skull and brain, and is absorbed by the chromophores O_2Hb and HHb, that have different absorption spectra. Assuming constant scattering, changes in concentration of these chromophores can be deduced, using the modified Lambert-Beer Law.(16,17) The measurements lump all haemoglobin concentration change from a volume of brain under the optodes. This volume might include all types of vessels. However, the actual vessel volume within the examined tissue is very small, and contribution of hemoglobin in conduit vessels to the NIRS signal are negligible. Total Hb (THb), the sum of O_2Hb and HHb, is associated with local cerebral blood *volume, whereas* O_2Hb is associated with local cerebral blood *flow*.(7)

We applied a continuous-wave NIRS device with 3 light bundles with wavelengths of 775 nm, 845 nm, and 904 nm (Oxymon, Artinis Medical Systems™, Zetten, The Netherlands). A fixed differential path length factor (DPF) of 6.6 (corresponding to age 50) was used in all subjects, which accounts for the increased distance travelled by light due to scattering.(16) At present, no data are available on the actual variation of the DPF with age above 50 years. Our control and patient group, however, were age-matched, which should reduce any systemic measurement bias induced by using a fixed DPF.

Data Acquisition

Subjects were in sitting position and received first a three-lead ECG for measurement of the interval between consecutive R-peaks (RR interval). BP was measured using a photoplethysmography cuff on the index or middle finger of the left hand (Finometer, Finapres Medical Systems, Amsterdam, the Netherlands), with the hand resting approximately at heart level supported by a sling. Data were collected by the Finometer for an uninterrupted period which lasted for a maximum of 5 minutes. Transcranial Doppler ultrasonography was used to measure CBFV. The left and right middle cerebral artery were insonated by placing a 2-MHz Doppler probe (Multi-Dop, Compumedics DWL, Singen, Germany) over the temporal window. The middle cerebral arteries were identified according to their signal depth, velocity, and wave characteristics.(18) If only one signal was available due to one-sided temporal window failure, we included this available signal for analysis. The probes were locked at a constant angle and position during data collection with a customized headband (Spencer

technologies, Seattle, WA, USA). Two pairs of NIRS optodes were placed and tightly fixed over the left and right frontal cortex in the same headband that locked the Doppler probes The midpoint between the horizontally positioned pairs was Fp1 for the left pair and Fp2 for the right pair, according to the international 10-20 electrode system. An interoptode distance of 5.0 cm was used to minimize contamination from the extra-cerebral circulation and to maximize the signal intensity.(16) NIRS cables and optodes were tightly fixed to prevent movement artifacts. Arterial saturation (SaO2) was recorded with a pulse oxymeter and end tidal CO2 (EtCO2) using a capnograph (N1000, Nellcor, Boulder, CO, USA). All data were sampled at 125 Hz.

Protocol

From twelve hours before the study, subjects refrained from caffeinated beverages and alcohol. They had a light breakfast at least two hours before the visit. All experiments were performed in the morning, in a quiet environmentally-controlled laboratory. After at least 30 minutes of sitting rest, spontaneous oscillations data were collected for 5 minutes. To assess the dynamic pressure-flow as well as the flow-brain tissue oxygenation relationship, spontaneous BP and CBFV oscillations were augmented using repeated sit-stand maneuvers at two different frequencies.(10) Subjects were instructed to perform repeated sit-stand maneuvers at 0.05 Hz (10 s sit followed by 10 s stand) for 5 minutes and at 0.1 Hz (5 s sit followed by 5 s stand) for 4 minutes. Verbal signs were given to facilitate repeated changes in body posture. The maneuvers were separated by 10 minutes for recovery.

Data Processing

All data were simultaneously recorded for offline analysis (Oxysoft, Artinis Medical Systems). A running average filter of 1 s was applied to the O_2Hb and HHb signals to increase the signal to noise ratio, and to reduce the heart beat and high frequency noise.(16,17)

Spectral analysis was performed on beat-to-beat mean BP, CBFV, O_2Hb, and HHb changes. The signals were aligned with the time of the R wave peaks of the ECG. The time series were then linearly interpolated at 2 Hz to obtain equidistant time intervals and detrended with third-order polynomial fitting. These data then were subdivided into 128 segments with 50% overlap and a Hanning-window was applied for spectral estimation. These data segmentations are based on a trade-off between a reduction in spectral variance and keeping sufficient spectral resolution. Each Hanning-windowed segment was fast-Fourier transformed and the periodograms were averaged to calculate the autospectrum of BP, CBFV, O_2Hb and HHb.(11)

For spectral analysis the following frequency ranges were chosen: the very low frequency (VLF) range: 0.02 – 0.07 Hz for spontaneous oscillations and for the induced 0.05 Hz maneuver, and the low frequency (LF) range: 0.07 – 0.13 Hz for spontaneous oscillations and for the 0.1 Hz maneuver.(10) Spectral power of oscillations was calculated as area under the curve (AUC) of the power spectral density plots. For comparisons, power spectral density plots of BP, CBFV, O_2Hb, and HHb were included if data on all signals were available for sitting rest and during both repeated sit-stand maneuvers.

The dynamic relation between BP as input and CBFV as output (BP – CBFV) and the dynamic relation between CBFV as input and O_2Hb as output (CBFV – O_2Hb) were determined with transfer function analysis during the repeated sit-stand maneuvers. Because of low coherence we did not include the calculation of transfer function during spontaneous oscillations of the above dynamic relationships and between CBFV as input and HHb as output (CBFV-HHb) during spontaneous and induced oscillations. Mean values of phase, gain, and coherence of the transfer function were analyzed in the same VLF and LF as described above. We have previously described the explanation of these estimates in detail.(5,9,10) In short, the phase shift quantifies the displacement in time of a signal relative to another. The transfer function gain determines the magnitude relationship between two signals. Coherence tests the linearity of the relationship between these signals. Coherence approaching unity in a specific frequency suggests a linear relationship, whereas coherence approaching zero indicates no relationship between the signals, severe extraneous noise, or a non-linear relationship.(19) A coherence of 0.4 is considered the lower limit where transfer function estimates can be calculated with confidence.(11) Estimates of phase, gain, and coherence were therefore only included if coherence was > 0.4. All analyses were performed with commercially available software (DADiSP, DSP Development, Cambridge, MA, USA).

Statistical Analysis

Data are presented as mean ± SD. Normal distribution was tested using Q-Q plots and could not be assumed for power spectral data of beat-to-beat mean BP, CBFV, 02Hb and HHb. Comparisons between the control and patient group were made using the independent samples *t* test and the Mann-Whitney's *U* test. For the comparisons of the transfer function estimates between both 0.05 Hz and 0.1 Hz maneuvers, a paired samples *t* test was applied. Statistical significance was set at $p < 0.05$. All statistical analysis were performed using statistical software (SPSS version 16.0, SPSS Inc, Chicago, IL, USA).

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of patients and controls at screening. Patients and controls were matched for age and blood pressure level at screening (Table 1). Specifically, 15 out of 21 AD patients and 14 out of 20 controls were hypertensive (BP > 140/90) at screening. More AD patients however, used anti-hypertensive medication (12 vs. 4) and 5 AD patients had diabetes mellitus type 2. As expected, patients had substantially lower cognitive tests scores and more hippocampal atrophy. The difference in age-related white matter score was not significant (Δ 1.9 on the 30 point scale, $p = 0.089$).

Baseline Hemodynamic Measurements

Table 2 provides an overview of the baseline hemodynamics under resting conditions. Heart rate (HR) and BP data could be obtained in all controls and patients. In 1 control and 4 AD patients, data on CBFV could not be obtained due to an insufficient temporal window. Additionally, in 1 AD patient the NIRS measurement had to be excluded because of a low signal-to-noise ratio. Although systolic and diastolic BP (sphygmomanometry) were comparable between AD and controls at screening, mean arterial pressure as obtained from the average of 5 min recording at rest using Finometer was higher in AD. Moreover, resting heart rate and spontaneous BP oscillations at the LF range of 0.1 Hz were higher in AD.

In patients with AD, despite the higher BP, CBFV was reduced by 10 % compared to controls. Consistently, there was a 34 % increase in cerebrovascular resistance index in AD (difference = 0.69 (0.25) mmHg/cm/s, $p = 0.012$) (Table 2). Alzheimer patients also had larger spontaneous oscillations in CBFV and O_2Hb at the LF range (Table 2).

Repeated Sit-Stand Maneuvers

Representative changes in BP, CBFV, and O_2Hb and HHb during baseline, and the 0.05 Hz and 0.1 Hz sit-stand maneuvers, are presented in Figure 1. Note that, as expected, O_2Hb and HHb oscillate in counter-phase, and further that these oscillations appear clearly related to the oscillations in BP and CBFV. Figure 2 shows the group averaged power spectra of controls and AD. The repeated sit-stand maneuvers induced oscillations in all signals (BP, CBFV, O_2Hb, and HHb), and the spectral power of these oscillations was significantly larger than for spontaneous oscillations in the corresponding frequency range (Figure 2). Notably, the 0.05 Hz repeated maneuver induced the most powerful oscillations. Power spectra for BP, CBFV, O_2Hb, and HHb were similar in AD and controls in the VLF and LF range (Table 3).

Table 1 Baseline Characteristics of Healthy Controls and Alzheimer's Patients

	Healthy Controls	Alzheimer patients
Age (years)	74.5 (2.8)	72.3 (5.7)
Gender (male : female)	14 : 6	9 : 12
BMI (kg/m^2)	24.8 (2.5)	24.5 (3.1)
BP sys (mmHg)	148.3 (20.0)	150.5 (18.9)
BP dias (mmHg)	83.3 (8.9)	80.1 (9.7)
CDR (range)	0	1.0 (0.5 – 2.0)
MMSE	29.3 (1.2)	21.3 (4.7) *
CamCog	NA	67.4 (13.4)
Use of antihypertensive medication	N = 4	N = 12**
Antihypertensive medication		
Diuretic	3	5
ACE Inhibitor	-	4
CA-Channel Blocker	-	2
Beta Blocker	2	7
AT II Antagonist	-	1
Smoking	N = 3	N = 2
Diabetes (Type 2)	N= 0	N = 5**
MRI		
MTA	0.44 (0.61)	2.00 (0.80)*
ARWMC	3.35 (3.12)	5.25 (3.09)

Values are presented as mean, with standard deviation in parentheses; CDR is presented as mean and range because the score is an ordinal value. BP was measured with sphygmomanometry at screening. MTA score [37], range 0–4; ARWMC score [38], range 0–30.
Key: ACE, angiotenstin converting enzyme; ARWMC, age-related white matter changes; AT II, angiotensin II; BMI, body mass index calculated as weight (kg) divided by height (m2); BP, blood pressure; CA, calcium; CamCog, cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly; CDR, clinical dementia rating; dias, diastolic; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; MTA medial temporal lobe atrophy; NA, not applicable; sys, systolic.
* $p < 0.001$, ** $p < 0.05$.

Figure 3 provides an example of the relation between the oscillations in BP and CBFV, and of the oscillations between CBFV and O_2Hb during 0.05Hz sit-stand maneuvers. During the maneuvers, oscillations in CBFV lead those of BP, whereas oscillations in O_2Hb follow those of CBFV (phase lag), suggesting a time delay between changes in CBF and brain tissue oxygenation.

Table 2 Baseline Hemodynamics in healthy controls and Alzheimer patients

	Healthy Controls	Alzheimer patients
Mean HR (bpm)	61.3 (5.8)	69.7 (11.8)*
Mean BP (mmHg)	78.8 (10.4)	87.6 (18.8)*
Mean CBFV (cm/s)	42.1 (9.9)	37.7 (14.7)
CVRi (mmHg/cm/s)	2.00 (0.55)	2.68 (0.97)*
$PetCO_2$ (mmHg)	34.7 (3.1)	35.2 (2.5)
BP VLF ($mmHg^2$)	4.62 (1.8)	7.42(4.8)
BP LF ($mmHg^2$)	1.19 (0.6)	2.29 (1.8)*
CBFV VLF ($(cm/s)^2$)	2.43 (1.3)	3.49 (1.3)
CBFV LF ($(cm/s)^2$)	0.55 (0.3)	1.29 (1.0)*
[oxyHb] VLF ($(\mu mol/l)^2$)	.038 (0.012)	0.084 (0.1)
[oxyHb] LF ($(\mu mol/l)^2$)	0.0091 (0.006)	0.037 (0.08)*
[HHb] VLF ($(\mu mol/l)^2$)	0.016 (0.009)	0.036 (0.05)
[HHb] LF ($(\mu mol/l)^2$)	0.0036 (0.003)	0.011 (0.02)

Average of 5 minutes measurement during sitting rest. For CBFV either the average of left and right, or the available signal were included for analysis. Values are presented as mean, with standard deviation in parentheses. oxyHb and HHb denote changes in concentration of frontal cortical oxygenated and deoxygenated hemoglobin, respectively. BP VLF, BP LF, CBFV VLF, CBFV LF, oxyHb VLF, oxyHb LF, HHb VLF, and HHb LF, spectral power of BP, CBFV, oxyHb and HHb in the very low frequency and low frequency range (VLF, 0.02– 0.07 Hz; LF, 0.07– 0.13 Hz).
Key: BP, blood pressure; CBFV, cerebral blood flow velocity; CVRi, cerebrovascular resistance index (mean BP/CBFV); HHb, deoxygenated hemoglobin; HR, heart rate; LF, low frequency; oxyHb, oxygenated hemoglobin; PetCO2, pressure of end-tidal CO2; VLF, very low frequency.
* $p < 0.05$.

No differences in transfer function gain and phase between BP and CBFV were observed between the controls and AD (Table 3). Transfer function gain between CBFV and O_2Hb was higher in AD during the 0.05 Hz repeated sit-stand maneuver, and the phase lag between CBFV and O_2Hb was larger (Table 3 and Figure 4). The use of antihypertensive medication in the control and AD group did not lead to within-group differences in gain and phase between CBFV and O_2Hb (p all > 0.1). The within-group differences for diabetes mellitus in the AD group could not be assessed, because 3 diabetic patients were excluded from transfer function analysis due to low coherence (that is, ultimately, only 2 patients with (type II) diabetes were included in the AD group for this part of the analysis).

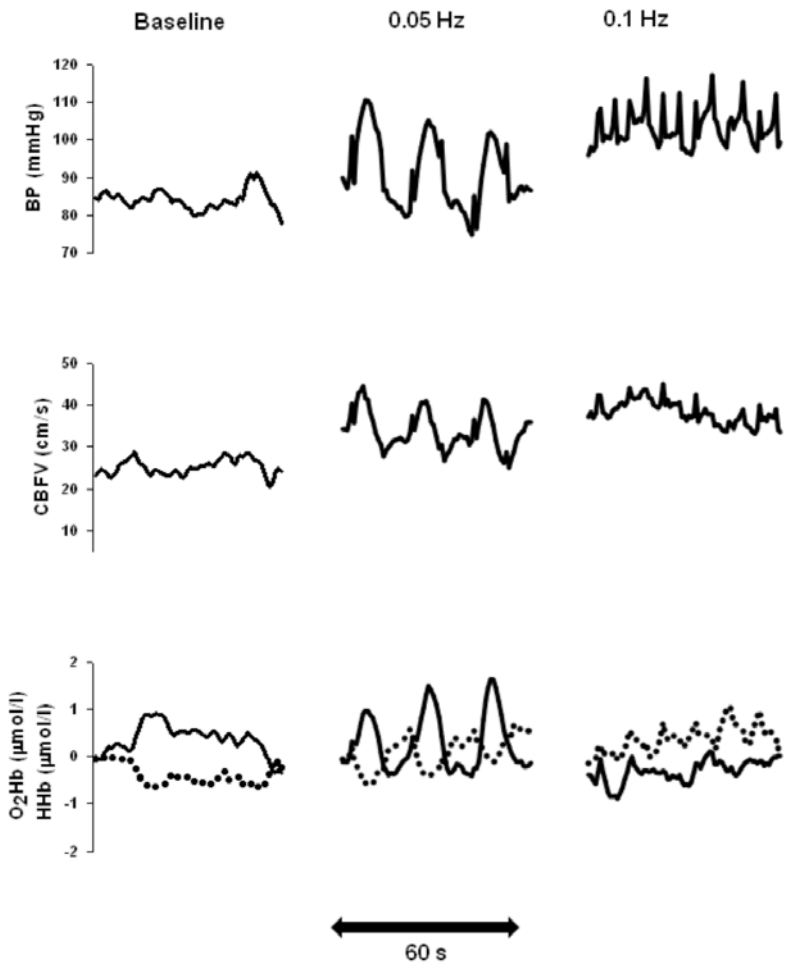

Figure 1 Example of blood pressure, cerebral blood flow velocity, and cortical frontal oxy- and deoxygenated hemoglobin oscillations in sitting rest and during the 0.05 Hz and 0.1 Hz repeated sit-stand maneuvers in 1 subject

Beat-to-beat data from 1 subject, variability in blood pressure (BP; upper panel), cerebral blood flow velocity (CBFV; middle panel) in the left middle cerebral artery, left frontal cortical oxygenated and deoxygenated hemoglobin (O_2Hb, solid line, and HHb, dashed line—both bottom panel), during baseline measurements in sitting rest (left panel) and the repeated sit-stand maneuvers at 0.05 Hz (middle panel) and 0.1 Hz (right panel). Note the enhanced amplitude and consistency of the oscillations induced by the 0.05 Hz repeated sit-stand maneuvers.

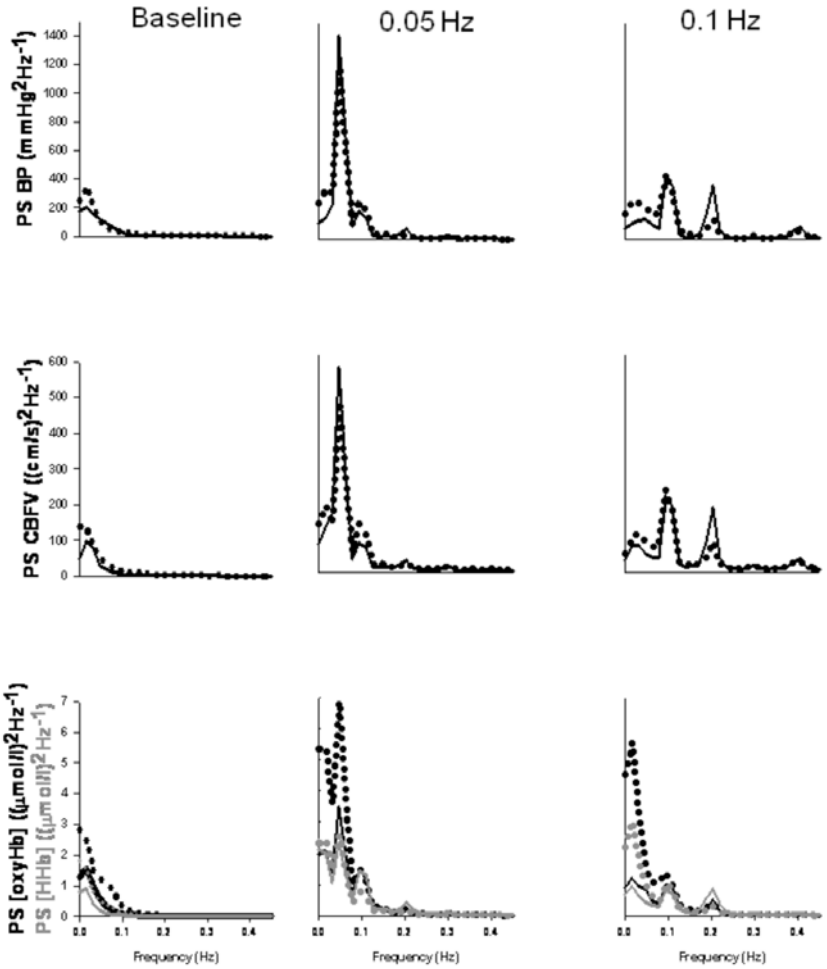

Figure 2 Group averaged power spectra of blood pressure, cerebral blood flow velocity, and cortical frontal oxy- and deoxygenated hemoglobin oscillations in sitting rest and during repeated sit-stand maneuvers

Results of spectral analysis of blood pressure (BP; upper panel), cerebral blood flow velocity (CBFV; middle panel), and frontal cortical oxygenated and deoxygenated hemoglobin (O_2Hb, black line, and HHb, gray line — both bottom panel) during sitting rest (left), the 0.05 Hz repeated sit-stand maneuver (middle), and the 0.1 Hz repeated sit-stand maneuver (right). The solid lines represent the spectra of the oscillations in healthy controls, the dotted lines are for the Alzheimer's patients.

Table 3 Hemodynamics in healthy controls and Alzheimer patients during two repeated sit-stand maneuvers

	Healthy Controls		Alzheimer Patients	
	0.05 Hz	0.1 Hz	0.05 Hz	0.1 Hz
Number of Subjects+	16	17	15	15
HR (bpm)	68.18 (7.3)	73.50 (7.0)	79.21 (13.5)*	85.45 (14.5)*
BP (mmHg)	91.27 (14.7)	93.05 (13.5)	105.64 (21.1)**	104.84 (21.5)
CBFV (cm/s)	46.43 (7.9)	46.45 (7.5)	40.79 (14.8)	43.53 (14.8)
$PetCO_2$ (mmHg)	34.23 (2.5)	34.24 (2.2)	34.01 (2.7)	33.8 (2.4)
PS BP ($mmHg^2$)	42.89 (19.1)	15.24 (7.19)	38.36 (26.0)	17.49 (13.8)
PS CBFV ($(cm/s)^2$)	17.28 (9.8)	7.63 (4.2)	18.72 (17.7)	8.24 (5.8)
PS OxyHb ($(\mu mol/L)^2$)	0.15 (0.08)	0.058 (0.047)	0.29 (0.2)	0.11 (0.16)
PS HHb ($(\mu mol/L)^2$)	0.10 (0.09)	0.036 (0.043)	0.12 (0.09)	0.043 (0.054)
TFA BP – CBFV++				
Number of Subjects	16	18	13	15
Phase (rad)	0.73 (0.29)	0.70 (0.23)	0.81 (0.24)	0.65 (0.21)
Gain (cm/s/mmHg)	0.55 (0.16)	0.60 (0.13)	0.47 (0.17)	0.62 (0.22)
nGain (%cm/s/%mmHg)	1.18 (0.29)	1.36 (0.25)	1.25 (0.30)	1.43 (0.31)
Coherence	0.65 (0.12)	0.76 (0.13)	0.68 (0.11)	0.77 (0.10)
TFA CBFV – oxyHb++				
Number of Subjects	15	16	10	10
Phase (rad)	-0.81 (0.29)	-1.14 (0.67)	-1.13 (0.44)	-1.11 (0.57)
Gain (μmol/L/cm/s)	0.076 (0.021)	0.084 (0.05)	0.13 (0.049)	0.078 (0.02)
Coherence	0.53 (0.086)	0.60 (0.10)	0.60 (0.13)	0.57 (0.11)

Average of 5 and 4 minutes repeated sit-stand at 0.05 Hz and at 0.1 Hz, respectively. For CBFV either the average of left and right, or the available signal were included for analysis. Values are presented as mean, with standard deviation in parentheses. PS BP and PS CBFV denote spectral power of BP and CBFV.

Key: BP, blood pressure; bpm, beats per minute; CBFV, cerebral blood flow velocity; HHb, deoxygenated hemoglobin; HR, heart rate; nGain, normalized gain; oxyHb, oxygenated hemoglobin; PetCO2, pressure of end-tidal CO2; PS, power spectrum; TFA, transfer function analyses.

+ Data were only included if measurements on all signals were available.

++ Data were only included if coherence of the transfer function was >0.4.

* $p < 0.01$.

** $p < 0.05$.

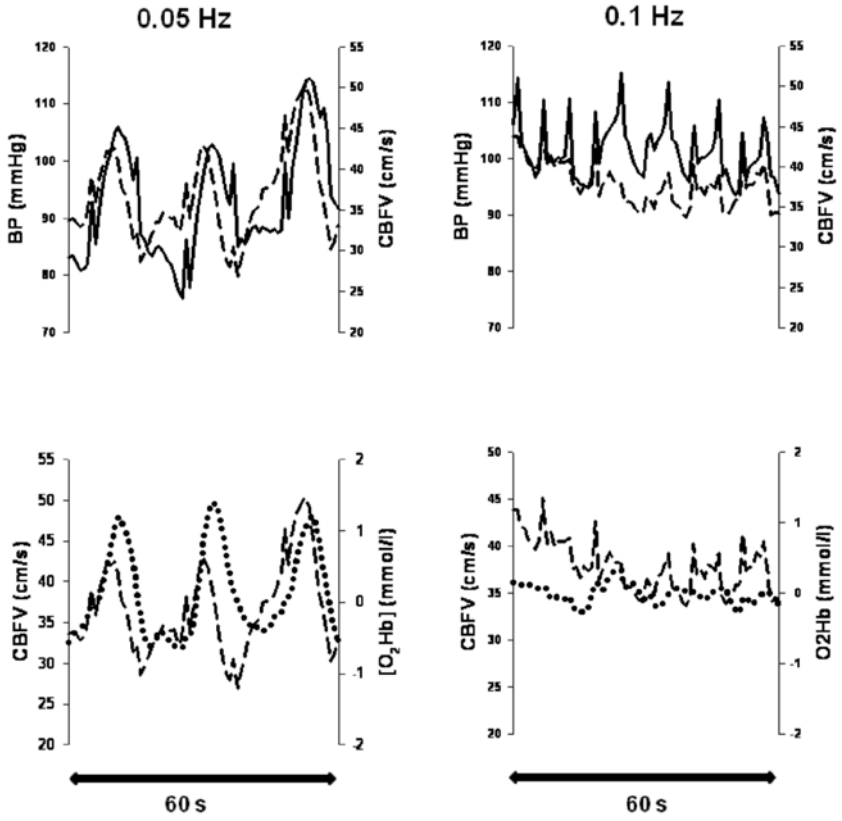

Figure 3 Example of the relation between BP and CBFV, and CBFV and oxygenated hemoglobin, during the repeated sit-stand maneuvers at 0.05 Hz

Representative data from 1 healthy control is shown. The left panel presents the BP and CBFV changes (upper panel) and the CBFV and oxygenated hemoglobin (O_2Hb; bottom panel) changes during the 0.05-Hz maneuver. The solid line represents changes in BP (upper panel), the long dashed line
represents changes in CBFV (upper and bottom panel) and the dotted line changes in O_2Hb. Note that CBFV leads BP, whereas O_2Hb lags behind CBFV. The data at 0.1 Hz are not shown because oscillations in O_2Hb were not as clear as at 0.05 Hz.

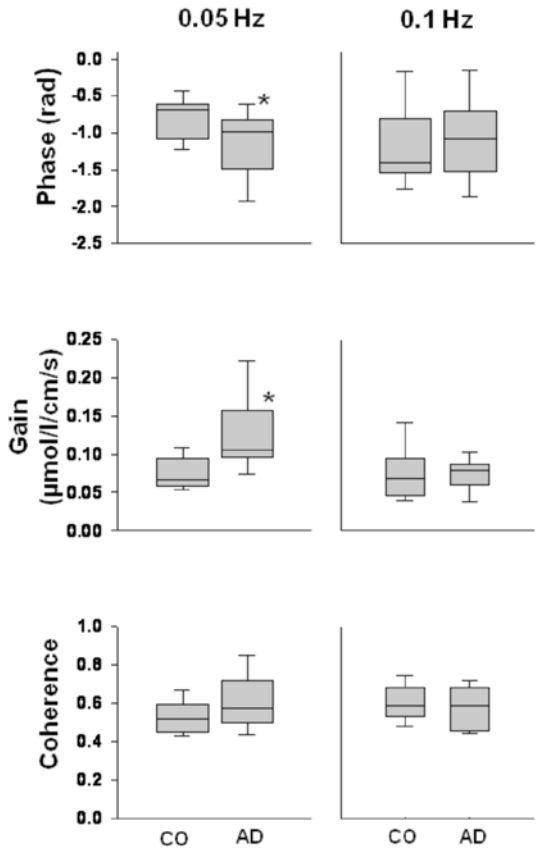

Figure 4 Transfer function analysis of cerebral blood flow velocity and oxygenated hemoglobin in the frontal cortex in healthy controls and Alzheimer patients

Values of transfer function analysis between cerebral blood flow velocity and oxygenated hemoglobin in healthy controls (CO) and Alzheimer patients (AD) in the very low (0.02– 0.07 Hz) and low (0.07–0.13 Hz) frequency range expressed in phase (upper panel), gain (middle panel), and coherence (bottom panel). Data of controls are presented left and of Alzheimer's patients right. The box plots represents group average values with the 95% confidence interval.
* $p < 0.05$ compared with healthy controls.

Discussion

This study assessed dynamic cerebral autoregulation in patients with Alzheimer's disease by means of the concomitant registration of changes in blood pressure, blood flow velocity in the middle cerebral artery, and cerebral frontal cortical oxygenation. There are three main findings in this study. First, in view of the fact that the origin of very low frequency oscillations in cortical oxygenation remains disputed, these data demonstrates that these oscillations are related to changes in global CBF, as measured in the middle cerebral artery, and that these CBF changes in turn were related to changes in systemic blood pressure. Second, this study shows that by using repeated sit-stand maneuvers, the dynamic CBF-brain tissue oxygenation relation can be assessed using transfer function analysis during repeated sit-stand maneuvers associated with a high coherence function (> 0.4) between these variables. Third, we have shown that how changes in CBF are transmitted to changes in brain tissue oxygenation differs essentially between patients with Alzheimer's disease and controls, as evidenced by increased transfer function gain and phase at 0.05 Hz between changes in CBF velocity and cortical O_2Hb signal.

Oscillations in Cerebral and Systemic Hemodynamics

The NIRS method directly assesses cerebral cortical oxygenation changes at the cerebral cortical tissue level. In accordance with the literature, we detected spontaneous oscillations in O_2Hb and HHb in the very low and low frequency range, where also spontaneous variability in BP and CBFV can be found.(6,20) Compared with healthy controls, AD patients had enhanced spontaneous oscillations in BP in the low frequency range (around 0.1 Hz), which led enhanced spontaneous oscillations in CBFV and O_2Hb, but not HHb.

The repeated sit-stand maneuvers induced large oscillations in O_2Hb that mirrored those in BP and CBFV. Thus far, only one study has succeeded in inducing oscillatory O_2Hb changes, using deep breathing at 0.1 Hz, and these authors observed similar oscillations in BP, CBFV and O_2Hb.(7) With a repeated sit-stand maneuver, we were able to induce oscillatory O_2Hb changes in the very low frequency of 0.05 Hz, which would not have been possible with deep breathing. Our data indicate that oscillatory O_2Hb changes in this frequency range are related to the oscillations in CBFV, which in turn are induced by oscillations in systemic BP. The larger oscillations in BP and CBFV at 0.05 compared to 0.1 Hz during repeated sit-stand maneuvers are in agreement with previous studies.(9,10,21) Taken together, the relationship between BP, CBFV and O_2Hb during repeated sit-stand maneuvers lends support to the notion that upstream oscillations in CBF induced by changes in BP contribute importantly to the downstream brain tissue level oscillations in O_2Hb.

CBFV and Dynamic Autoregulation

Confirming previous results from a pilot study measuring only CBFV, we observed that CBFV was reduced and cerebrovascular resistance was increased in AD.(4) This may be explained by enhanced vasoconstriction and other vascular factors such as a reduced cerebral capillary density and an aberrant vascular repair.(22)

We have previously shown that this difference could not be explained by differences in individual whole brain volume.(4) We could however, not reproduce the earlier findings of a lower gain between BP – CBFV during either the 0.05 Hz or 0.1 Hz repeated maneuver in AD relative to controls. An important difference between these studies is that in the present study, patients were not treated yet with cholinesterase inhibitors. These drugs potentially alter cerebral hemodynamics.(23) Moreover, AD patients in the present study were older.

The CBF response to transient changes in BP, as quantified by transfer function gain and phase, reflects dynamic cerebral autoregulation.(11) The mechanisms underlying dynamic autoregulation are not clear. The unaltered gain and phase between BP and CBFV observed in this study suggest that dynamic autoregulation –at least at the macrovascular level- is preserved in patients with AD. However, dynamic cerebral autoregulation was impaired in the mouse models of AD related to beta amyloid pathology.(2,3) These discrepancies may highlight the differences in the regulation of cerebral hemodynamics between patients with AD and the animal model used. Clearly, further work is needed to understand the regulation of CBF and its relation to AD pathology.

The Dynamic CBFV- O_2Hb Relationship

The dynamic relation between oscillations in CBFV and cortical O_2Hb may reflect a regulatory mechanism to maintain brain tissue oxygenation homeostasis.(3,17) However, the investigation of the relationship between spontaneous oscillations in CBFV and O_2Hb using transfer function analysis suffers from the weakness and non-stationarity of the O_2Hb measurement under resting conditions.(17) The repeated sit-stand maneuvers in this study induced large oscillations in BP, CBFV, and O_2Hb and enhanced coherence between CBFV – O_2Hb (> 0.4) and therefore improve the reliability of the transfer function analysis.(5)

CBFV was measured in the MCA. NIRS measurement was obtained from the medial-frontal cortex areas which are dependent for their blood supply on the anterior cerebral artery (ACA) as well as the MCA. We assumed that relative change of CBFV in the MCA would be the same for the relative change of CBFV in the ACA in response to a change in blood pressure.

O_2Hb oscillations seem to follow those of CBFV (Figure 3). Therefore, the phase difference between these variables may reflect a transit time between flow in supplying brain arteries and O_2Hb. In patients with AD, a disease in which it becomes progressively clear that the cerebral microvasculature is affected, we identified a larger phase lag and higher gain between CBFV and O_2Hb at the very low frequency of 0.05 Hz –where dynamic cerebral autoregulation is active- but not in the low frequency (0.1 Hz) –where autoregulation is less active.(24) Because O_2Hb is a correlate of local blood flow, this might point to a differential transfer of central blood flow to local blood flow and to local cerebral oxygenation in Alzheimer's disease. Whether this is due to differences in active regulation mechanisms or due to differences in the passive properties of the cerebral vasculature is not clear.(25) The increases in the transfer function gain between CBFV and O_2Hb provide further insights into the cerebral microvascular function in AD. Using positron emission tomography (PET), it has been shown that the oxygen extraction fraction, regarded as an indicator of the brain tissue metabolic reserve, was increased in AD (a reduction of metabolic reserve).(8) In addition, reduced brain metabolic rate for glucose and oxygen has been observed in AD which may reduce the oxygen diffusion gradient from the capillaries to brain tissue. Therefore, the increase in CBFV - O_2Hb gain might also reflect a reduced metabolic reserve or a reduced diffusion of oxygen leading to enhanced oscillations in [O_2Hb] in response to changes in CBF.

The specific mechanisms for the altered CBFV – O_2Hb relationship in AD cannot be determined in this study. Amyloid beta, the peptide linked to the pathological manifestations in AD, causes cerebrovascular dysfunction 2 as well as deposits in the small vessels in AD (cerebral amyloid angiopathy). In turn, the brain microcirculation not only responds to amyloid beta, but also regulates amyloid beta.(26) It is possible that these abnormalities may contribute to the altered CBFV- O_2Hb relation. Further, the enhanced oscillations of O_2Hb in response to changes in CBF may lead to local hypoxic changes in the brain that in turn could establish a vicious circle: over expression of transcription factors in smooth muscle cells of small brain arteries promote a hypercontractile phenotype of cerebral arteries, which may increase the CVR, and in turn leads to hypoxia.(27)

Study Limitations

Significantly more patients however used antihypertensive drugs. However, cerebral autoregulation and cerebral blood flow are preserved during treatment with β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, AT1-recepter blockers, or thiazide diuretics.(28-32)

In the AD group, 5 subjects suffered from type 2 diabetes mellitus. Data regarding the influence of diabetes mellitus on cerebral autoregulation are mixed, reporting either an impairment or preservation of cerebral autoregulation. (33-35) For the analysis of the relation between CBFV – O_2Hb at 0.05 Hz -where the current study demonstrated an altered relationship in AD-, only 2 diabetic AD patients were included. This makes a confounding effect of diabetes on our findings very unlikely.

Moreover, hypertension and diabetes mellitus are the most important vascular risk factors for AD(36), and exclusion of AD patients with such comorbidities from studies would seriously hamper their generalizability .

Both methods to assess cerebral perfusion, TCD and NIRS, have certain limitations that have been well described in the literature and that are summarized in the Methods section. We combined these two measurements to provide information on both global cerebral perfusion and brain tissue level oxygenation in patients with AD.

Conclusion

Using a unique combination of Finapres, TCD, and NIRS measurements, we have shown that oscillations in cerebral blood flow velocity, induced by repeated changes in body posture, translated into large oscillations in cerebral cortical oxygenation. Furthermore, the dynamic relation between cerebral blood flow velocity and cerebral cortical oxygenation can be assessed using transfer function analysis during repeated sit-stand maneuvers. Finally, we demonstrated that Alzheimer patients differed from controls in how these changes in flow were transmitted to changes in cerebral cortical oxygenation. This result might be indicative of either altered properties of the cerebral microvasculature or brain tissue oxidative metabolism in patients with Alzheimer's disease.

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Chapter 7

Summary and discussion

Summary

This thesis started with Mrs. X. Her case gave rise to the following questions. In short, do orthostatic hypotension (OH), postprandial hypotension (PPH), and carotid sinus hypersensitivity (CSH) share a common pathophysiology and do they predict mortality? Does the blood pressure (BP) decrease directly after standing, but also the degree of BP recovery afterwards, predict mortality? Does Alzheimer's dementia (AD) affect BP regulation through the baroreflex sensitivity (BRS) and does cholinesterase inhibitor use influences this BRS? And finally, does AD impair dynamic cerebral autoregulation? The answers are given in the summary below.

OH, PPH and CSH are disorders of BP regulation with high prevalence in the elderly. The exact pathophysiology of these hypotensive syndromes is not clear and rarely studied together. The cardiovascular autonomic system plays an important role in the short-term regulation of BP. In **Chapter 2a** we compared 14 different non-invasive autonomic function indices of heart rate variability (HRV), BP variability (BPV), and BRS in a cohort of 203 patients visiting our falls and syncope outpatient clinic. We found no differences of these measures in geriatric patients with hypotensive syndromes compared to geriatric patients without these hypotensive syndromes. Patients with and without falls, dizziness, or syncope as presenting symptom did not show differences in these indices either. These findings argue against a single or dominant etiological factor, i.e. autonomic dysfunction, in the etiology and pathophysiology of these hypotensive syndromes. It also underscores the need for a multifactorial approach in diagnostic investigations of elderly with falls and/or syncope.

In **Chapter 3a** we applied an alternative approach to study whether there is indirect evidence for a shared similar pathophysiology in OH, PPH and CSH. Therefore we examined the occurrence of these three syndromes in a cohort of 313 patients visiting our falls and syncope outpatient clinic (this cohort includes the 203 patients of chapter 2). We studied the co-occurrence of OH, PPH, and CSH in the same patient and determined, if it occurred more often than chance. Although OH, PPH, and CSH had a high prevalence of 54%, 58%, and 53%, respectively, and occurred frequently together in the same patient, there was no clustering of these syndromes. This absence of clustering of hypotensive syndromes in the same patients suggested different underlying pathophysiological mechanisms for the different hypotensive syndromes. Besides clustering, we also studied the impact of the three hypotensive syndromes on all-cause mortality. During a median follow-up of 23.0 months, 58 (19%) patients died. We found that OH, but not PPH or CSH, predicted mortality (hazard ratio: 1.97; 95% confidence interval: 1.11-3.47). This relationship was no longer significant after

adjusting for age, comorbidity and other baseline characteristics. However, OH with a severe DBP decrease of 20 mmHg or more remained a powerful independent predictor of mortality (hazard ratio: 2.50; 95% confidence interval: 1.20-5.22), and therefore might be used prognostically as an easily available cardiovascular sign of increased mortality risk.

While the previous chapter looked at the influence of BP decline between 1 and 3 minutes after standing (OH) and mortality, **Chapter 4** investigated the association of mortality with BP decrease and recovery in the first minute directly after standing. This was done in a cohort of 238 patients visiting our falls and syncope outpatient clinic as part of the larger cohort of 313 patients described in chapter 3. During a median follow-up of 21.0 months, 36 (15%) patients died. Systolic BP (SBP) and DBP decreased maximally with 42 ± 25 mmHg and 23 ± 15 mmHg, respectively, from baseline within the first 15 seconds directly after standing, corresponding with 75 ± 15% and 71 ± 16% of the baseline SBP and DBP. Neither the absolute nor the relative initial BP drop after standing predicted mortality. However, the percentage of BP recovery 40 to 60 seconds after standing was associated with mortality, even after adjustment for age, comorbidity and other baseline characteristics. SBP recovery of less than 80% from baseline after 60 seconds was a powerful independent predictor of mortality (hazard ratio: 3.00; 95% confidence interval: 1.17-7.68).

AD is a frequent occurring progressive neurodegenerative disorder which places a huge burden on society and individual caregivers. Cardiovascular factors are commonly accepted as risk factors for AD, however, the exact relationship between these factors and AD remains poorly understood. The cholinergic system is an important component of cardiovascular and autonomic control, including the baroreflex and this cholinergic system is known to be affected in AD. Therefore, in **Chapter 5a** we studied the baroreflex in 18 AD patients, 11 patients with mild cognitive impairment and 19 age and sex matched healthy controls. The baroreflex was reduced in AD compared to patients with mild cognitive impairment and the healthy controls. This result was reproduced in an independent validation sample of 16 AD patients, 18 patients with mild cognitive impairment and 19 age and sex matched healthy controls. Treatment of 18 AD patients with acetylcholinesterase inhibitor increased baroreflex sensitivity with 66%. In summary, the baroreflex is reduced in AD and increases after treatment with acetylcholinesterase inhibitor. The pathophysiological and diagnostic value of this association between impaired baroreflex and AD needs further research.

Finally in **Chapter 6**, the association of AD with dynamic cerebral auto-regulation and brain tissue oxygenation was studied. In 21 patients with mild to moderate AD and 20 age matched controls, we investigated how oscillations in

cerebral blood flow velocity (CBFV) and O_2Hb are associated with oscillations in BP induced through repeated sit-stand maneuvers at 0.05 Hz and 0.1 Hz. In AD, cerebrovascular resistance was 34% higher, compared to the age matched controls. Despite a higher cerebrovascular resistance, there was no difference in dynamic autoregulation between patients with AD and healthy control. However, in patients with AD, the translation of CBFV to O_2Hb essentially differed from age matched healthy controls. In AD, these results of an elevated cerebrovascular resistance and an altered transfer of cerebral blood flow to cortical oxygenation, might indicate altered properties of the cerebral microvasculature or altered brain tissue oxidative metabolism.

General discussion

The studies conducted in this thesis are part of an active, ongoing scientific debate on the causes of syncope and falls on the one hand, and the age related changes in pathophysiology and prognosis of blood pressure and cerebral perfusion regulation disturbances on the other. We strongly felt that participation in this scientific debate stimulated our own scientific work and was an essential part of it, and therefore wrote several letters to the editor and to our research colleagues, which are also part of this thesis. Together they give an impression of hypotheses tested by fellow researchers, and show that our work fits well in the highly relevant and urgent quest for better understanding of the specific age-related changes in homeostasis of hemodynamics in our aging societies.

In **Chapter 2b** we positioned our work in the debate on the relevance of the mono-causal oriented adenosine 5′-triphosphate testing in a heterogenic geriatric falls population with multicausal etiology.(1,2) Our letter highlights methodological issues of the representativeness of the studied research population. This issue of external validity or generalizability of the presented research results of this thesis, always a key-question in valueing aging and geriatric research studies, will be put into perspective and discussed further in the section **Methodological considerations** below.

In **Chapter 3b** we argue in another letter that besides visit-to-visit BPV, the postural or postprandial change of BP might also contain additional prognostic information.(3,4) In **Chapter 3c** we questioned the prognostic meaning of the change of postural DBP in middle aged adults on mortality.(5,6) In **Chapter 5b** the potential additive prognostic information of BPV above and beyond mean BP is suggested for white matter hyperintensities and cognitive decline in older people.(7,8) These three chapters have prognostication in common and the prognostic information of the presented research results of this thesis will be

discussed in a broader context in the section **Clinical (and research) implications** below.

Methodological considerations

This thesis investigated a selective patient population of 313 patients who were referred to an out-patient geriatric falls and syncope clinic, because of syncope, falls and/or dizziness. This has the disadvantage of a specific selection and therefore our sample is not a representative for the general population, but only for populations referred to similar outpatient clinics. Between 30 % and 40 % of community dwelling adults aged 65 years or older fall at least once per year.(9) Only a fraction of these older adults visits a general practitioner or emergency department and of those also only a fraction is referred to a fall clinic. The source of referral to a fall clinic (general practitioner or emergency department), has substantial influence on the case-mix.(10) This highly selective nature of falls and syncope patients referred to the fall clinic, in contrast to the general elderly population is highlighted in Figure 1.

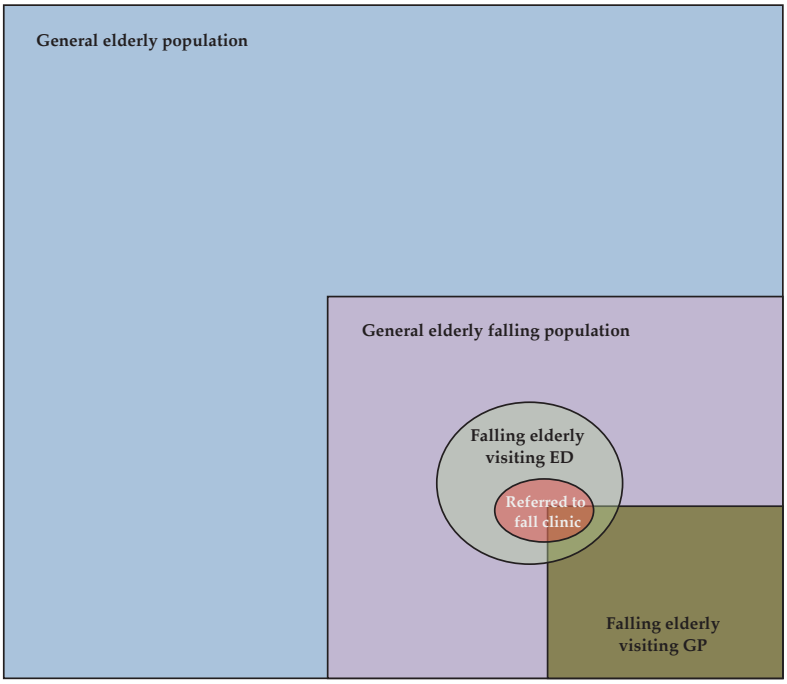

Figure 1 Venn diagram of elderly (falling) population

GP, general practitioner; ED; emergency department.

The 313 patients we studied represent a very heterogeneous study group. Importantly, they were all patients referred (merely all by the general practitioner) to our academic falls and syncope outpatient clinic. Next, patients were only excluded if they were not able to follow the instructions, could stand for 10 minutes and could drink a test meal of 200 ml within 10 minutes. Patients were not excluded because of certain diseases (for example heart failure, diabetes mellitus, Parkinson's disease or dementia), organ dysfunctions (for example renal failure) or age. Although heterogeneous, this prevented underrepresentation of certain patient characteristics in the research population as has been observed in the representation of elderly in cardiovascular, oncologic or pharmaceutical clinical trials.(11-14) Of the 313 patients, two rather large groups were excluded in the two studies investigating mortality. First, in **Chapter 3a**, carotid sinus massage (CSM) was not performed in 41 (13%) patients because they met the exclusion criteria. Accepted contraindications were taken as exclusion criteria for CSM: a murmur over the carotid artery, myocardial infarction, cerebral ischemia in the past 3 months, or a history of ventricular tachyarrhythmia's.(15). Second, in **Chapter 4**, 71 patients were excluded because there were no raw data files, due to theft of the test laptop before back-up. This was thought to be a random selection.

Table

Variable	CSM+ (n=272)	CSM- (n=41)	Raw data+ (n=242)	Raw data- (n=71)
Age	78.0±8.1	83.1±6.3*	78.4±7.9	79.7±8.5
BMI	26.5±4.4	26.0±4.0	26.5±4.6	26.0±3.9
Female, n(%)	61%	73%	64%	59%
Baseline SBP	168±25	175±33	168±26	173±27
Baseline DBP	78±12	79±12	79±12	79±13
Baseline heart rate	67±11	74±13*	68±12	68±12
CIRS-G total score	11.2±4.6	12.5±4.4	11.1±4.5	12.3±4.9†
Hazard ratio	1	2.97 (1.71-5.14)	1	1.43 (0.82-2.50)
Hazard ratio, adjusted	1	1.72 (0.91-3.26)	1	0.98 (0.54-1.78)

Results are reported as means ± standard deviations or numbers (percentages). Age(years); BMI, body mass index(kg/m^2); BP, blood pressure(mmHg); heart rate(beats per minute); CIRS-G, Cumulative Illness Rating Scale for Geriatrics. ***:**significant differences ($p<0.05$) between patients with and without CSM; **†:**significant differences ($p<0.05$) between patients with and without the availability of the raw data files.

The table above compares the baseline variables of patients with and without CSM and the with or without the availability of the raw data files. Patients who were excluded for CSM were older and had a higher baseline heart rate. There was also a tendency to higher comorbidity burden, higher SBP and more female sex, but these differences were not significant. The patients of whom the raw data were stolen had higher comorbidity burden and a tendency to be older en a higher SBP but these differences were not significant. The unadjusted hazard ratio for mortality among the "stolen" patient population had a tendency to be higher than the subpopulation with availability of the raw data, however this was also not statistically significant. After adjusting for baseline variables the hazard ratio decreased to unity. Although this stolen data were assumed to be a random selection, the populations differed on some aspects of baseline variables. Nevertheless, after correction for these differences there was no difference in mortality, which supports the assumption that it was a random selection, free from selection bias or bias by indication. On the other hand, the population in which no CSM was performed also differed in baseline characteristics with respect to the subpopulation of patients in which CSM was performed. Here the unadjusted hazard ratio for the subpopulation without CSM was much higher than the subpopulation of patient where CSM was performed. Even after correction for baseline variables this tendency remained, but was no longer statistical significant. This might point at residual confounding by indication; the population which was excluded for CSM was not only different at baseline, but might also be at higher risk of mortality by other factors than the baseline variables. Unfortunately, this reasoning cannot be completely evidenced because the tendency to a higher hazard ratio after correcting is not statistically significant. This might be due to the relative small studied population and for this comparison the study probably is underpowered. Because of the patho-physiology and prognosis related mechanisms of the selection, it is likely that in the CSM case, absence of evidence is not the same as evidence of absence.

To illustrate the possibility that the sample size is relatively small to extract all information, we extended some analyses of **Chapter 3a**. In this study, the association of the amount of SBP and DBP decrease during testing for OH on mortality was investigated. Therefore SBP and DBP decline subgroups were defined as a decline of < 20 (no OH), 20 to 35, and ≥ 35 mmHg for SBP and a decline of < 10 (no OH), 10 to 20, and ≥ 20 mmHg for DBP, respectively. We showed that DBP decline of ≥ 20 mmHg was independently associated with mortality, whilst SBP decline was not associated with mortality. We repeated the same analysis for SBP and DBP as a continuous variable. After correction for the baseline variables, the hazard ratio per 10 mmHg decrease of SBP and DBP was

1.09 (1.01-1.17) and 1.25 (1.06-1.49), respectively. This indicates that SBP decrease is associated with increase in mortality, although to a much smaller degree than DBP decrease. Besides the relative small sample size, this example also illustrates the loss of information by using categorized variables compared to continuous variables in this analysis.

Another consequence of a relative small sample size is the limiting amount of covariates which can be used. In **Chapter 3a** there were 58 events and we used the covariates age, gender, BMI, comorbidity (CIRS-G score), medication use and baseline SBP and DBP. Medication use consisted of 9 medication groups, so in total 15 covariates were used, i.e. approximately 4 events per covariate. When excluding medication use, or replacing it for polypharmacy (using 4 or more medications), the total covariates used changed to 6 or 7, i.e. approximately 8-9 events per covariate. This did not change the main results. In **Chapter 4** there were 36 events and we used 7 covariates, i.e. approximately 5 events per covariate. Although as a rule of thumb often approximately 10 events per covariate is claimed to be necessary, there is evidence that this can be lowered to 5-9 or even less events per covariate, without losing accuracy and validity in the control of confounding.(16) As a consequence of our sample size, we arrived at the limit of covariate correction in our analyses, which is often the case in studying older populations with comorbidity and high levels of hetereogeneity.

The 313 patients in our study represent a rather frail and vulnerable geriatric population group with a mean age of 79 ± 8 year and a CIRS-G comorbidity score of 11.4 ± 4.6. In comparison, a population of 252 patients ≥ 75 year on a general geriatric rehabilitation unit had approximately the same CIRS-G comorbidity score, but had a substantially higher mean age of 85 years.(17) In contrast, a population of 102 hip fracture patients aged ≥ 65 year admitted on a geriatric rehabilitation unit and a population of 212 patients aged ≥ 65 year admitted on a acute geriatric ward were of approximately the same mean age of 79 and 81 year, respectively, but had a substantially lower CIRS-G comorbidity score of 9.9 and 9.2 respectively.(18,19)

In summary, the external validity from our findings to the general elderly population is limited. However, the geriatric population visiting the falls and syncope clinic is the population with the highest relevance of hypotensive syndromes and therefore our research results are applicable to those patients with the restriction that they have approximately the same baseline characteristics (i.e. age and comorbidity). In sum, our results probably hold true for the most frail older subjects with falls and related blood pressure regulation disturbances, which is an understudied population so far.

Clinical (and research) implications: prognostics

As mentioned above in the general discussion, one of the main potential implications of the presented research in this thesis lies in prediction. Prediction of mortality on the one hand and prediction of Alzheimer dementia on the other. Some additionally remarks will be made on the subject of prediction and prognostics below.

The following characterization, made in 1934, of prognosis remains still accurate today: "Of the three great branches of clinical science -diagnosis, prognosis, and treatment- prognosis is admittedly the most difficult. It is also that about which least has been written and of which our knowledge is least systematized."(20) This undervaluing of prognostic research lasts until now. Just very recently Hemingway et al.(21) argued for the recognition of the importance of this scientific domain and strongly plead for improved methodology. Of the four forms of prognostic research themes, two were addressed in the papers presented in this thesis:

- Specific factors (such as biomarkers and BP changes after standing) that are associated with prognosis (prognostic factor research)
- The development, validation, and impact of statistical models that predict individual risk of a future outcome (prognostic model research, eg the regression models found in our studies)

Despite the difficulty of adequate prognostic validation studies, which are often time consuming and thus expensive, they are increasingly important, especially in geriatric patients who encounter a shrinking horizon of their life expectancy.(22) Guidelines increasingly incorporate life expectancy as a central factor in weighing the benefits and the burdens of tests and treatments.(23) However, geriatric assessment is time-consuming and other medical specialists are not trained for this kind of assessment, therefore geriatric assessment has not typically been used in daily practice to assist in decision making. Therefore, there is increasing interest in finding predictors that are easy applicable, non-invasive, time efficient, cost-effective and have low patient burden as in clinical practice simpler models are more practical.(24) Studenski et al. impressively showed that gait speed, additive to age and sex, was as accurate in predicting survival in older adults as age, sex, walking aid use and variables of functional status, especially after age 75 years.(25) Similarly, in predicting morbidity and mortality following cardiac surgery, gait speed was at least as strong as a predictor as far less efficient traditional cardiac measures (eg. ejection fraction and composite cardiac risk scores).(26) In aging, BP does not tell it all and becomes a "poor story teller", hence the need for alternative simple, non-invasive risk factors like for example pulse wave analysis or velocity(27) or blood pressure variability.(4,28) In the light of this need for simple, but

informative predictors, BP decline after standing might be a candidate predictor because it has additional prognostic information above age, sex, comorbidity and BP.

Syncope can be classified in three groups: reflex or neurally-mediated syncope, syncope due to OH and cardiac syncope.(29) Patients with reflex syncope have a normal prognosis, whilst patients with a cardiac syncope have a higher mortality risk.(30) Also middle aged patients with syncope due to OH have a higher mortality risk.(31) Our results are in line with these observations, as PPH and CSH are classified as neurally-mediated syncope(29) and not associated with mortality, whilst OH is in elderly patients still associated with an increased mortality. After correcting for baseline variables this association is no longer statistical significant. However, the amount of SBP and DBP drop during OH measurement remains significantly associated with mortality as is the case for SBP and DBP in middle-aged persons.(5,6) From our results no conclusions can be drawn about causality. Cause specific mortality might help, but is not conclusive. Mortality through injuries is likely, but not necessarily, caused by OH. Moreover, the association between OH and cardiovascular disease can be both cause and effect. Thus, a dual role of orthostatic hypotension in prediction of adverse events, both as the causal factor and as an independent marker of underlying diseases is most likely.(32) Our result of the association of impaired BP recovery directly after standing and mortality, shows that BP regulatory systems are affected and that this dysregulation predicts mortality. Our results are in line with findings in 374 patients aged 70.2 ± 8.5 years of one primary care practice, in which inappropriate recovery was prognostically more important than the immediate blood pressure fall itself after standing.(33)

As mentioned above, we compared in **Chapter 2a** 14 different non-invasive autonomic function indices of HRV, BPV and BRS and we found no differences of these measures in geriatric patients with hypotensive syndromes compared to geriatric patients without these hypotensive syndromes. Although we studied the association between mortality and hypotensive syndromes, we did not study the association of these indices with mortality. The clinical relevance of diminished HRV preceding fetal death was first recognized in 1963.(34) HRV and BRS have significant prognostic value, independently of left ventricular ejection fraction, in patients with a recent myocardial infarction.(35) Also in an elderly population of 72 ± 6 years, HRV measures offers prognostic information independent of and beyond that provided by traditional risk factors.(36) However, in a general population, blood pressure variability did not incrementally predict outcome over and beyond mean systolic blood pressure.(37) We studied the association of these indices with mortality. All 5 HRV indices, none of the 4 BPV indices and 2 (SD-BRS and SQ-BRS-) of the 5 BRS indices were significantly

associated with mortality (for explanation of these indices see **Chapter 2a**). After correction for age, sex, BMI, comorbidity and baseline SBP, DBP and heart rate this association remained significant for 3 (RMSSD-HRV, LF-HRV and HF-HRV) of the 5 HRV indices and SQ-BRS- as BRS index. This remained the same even after further adjustment of the DBP decrease during OH testing (**Chapter 3a**) and/or percentage SBP recovery 55-60 seconds after standing (**Chapter 4**).

In conclusion, besides certain BP indices after standing up, also certain HRV indices measured during rest, can be used as easy applicable, non-invasive prognostic factors which contain additional prognostic information above age, sex and comorbidity.

Another form of prognosis or prediction, is the diagnostic prediction of AD. How should BRS as potential biomarker of AD be interpreted and implemented? We validated the discriminatory role of BRS for AD using an independent data set. In **Chapter 2** we determined HRV, BPV but also BRS indices in a elderly falls population. Of this population 6% was diagnosed with any form of dementia. We found no differences in HRV, BPV or BRS indices between falls patients with and without dementia. This is possibly due to the small sample of falls patients with dementia, the mixed etiology of dementias and because another method was used to determine BRS than in **Chapter 5a**. For a clinically meaningful interpretation, the BRS should not be interpreted on its own, but should be instead weighed against the previous probability of AD, which the clinician derives from interpretation of a combination of history taking, physical examination, neuropsychological evaluation, and neuroimaging.(38) A common limitation in dementia research for the use of BRS is that the clinical diagnosis is used as a reference standard. Because the clinical diagnosis is the reference standard, it is difficult to assess the potential influence of BRS on this clinical diagnosis, as it is not yet part of this clinical diagnosis. More prospective research is necessary to answer this question and to determine the potential role for BRS in the diagnosis of AD.

Future perspectives

Life is a highly organized complex state of an organism, operating in an equilibrium that is far from stable, yet sufficiently robust to resists the permanent attacks from its environment. During aging the capability to resist these environmental attacks diminishes and the system often enters a state of increased vulnerability to poor resolution of homeostasis after a stressor event, also defined as frailty.(39) As populations are quickly aging, the prediction of the reserve capacities, and improvement in the prognostication of mortality and

functional performance are of crucial importance for medical decision making both at the level of the individual patients and the society.

The human body has the structure of a network of coupled dynamical systems. Organs such as the heart, lungs and brain are highly clustered networks that are interconnected with each other by a few long range edges like the humoral system and autonomic neuronal system. The structure of for instance the His-Purkinje neural network(40) and the bronchial tree(41) is that of a scale free power law network.(42,43) Besides the complex structure, the function of different organs also exhibit complex dynamics like for example the regulation of heart rate(44-46), respiration(47), gait(48,49) and temperature.(50) Loss of this complex dynamic behavior can predict sudden cardiac death(51) and is associated with a breakdown in cognition.(52) Thus, network-theoretical properties appear useful as biomarkers of physiologic aging and therefore are likely to be valid measures of frailty.(53,54) Frailty is a state of critical loss of physiological complexity that results in heightened vulnerability to stressors.(54) Frailty and aging are characterized by the accumulation of deficits over time. Deficits can be defined as abnormalities of body areas and human behaviour and can include variables on physical function, psychological function, cognitive function, comorbidity, and health attitudes.(55,56) There is evidence for a limit in the maximum of deficit accumulation.(57) When this limit is crossed it seems not reconcilable with life in the long run, but patients may stay a longer period on this edge of frailty instability. Further loss results in a breakdown of the system with abrupt transitions like geriatric syndromes as falling, delirium or even a cascade of malfunctioning organs, and ultimately death. Therefore, frailty, being a state of critical loss of complexity, is increasingly studied by nonlinear models.(58-60) Slowing down of recovery time is an early warning signal of approaching abrupt critical transitions (tipping points) in complex systems.(61-66) From the emerging field of complex system biology, there is firm experience and evidence for critical slowing down as an early warning signal in physics, chemistry, climate changes and ecology(62,67-71), however the use and evidence in medicine is sparse. In medicine, critical slowing down of recovery may be used to rank complex organ systems on a broad scale from resilient to fragile, and may be used as early warning signals for closeness to a tipping point both in normal physiology and in chronic disease. The results of **Chapter 4** can be seen as an example of slowing down of SBP recovery, and hence loss of complexity and higher mortality. For clinical practice, the simple maneuver of standing up is an excellent stress test and perturbation of the neuro-cardiovascular system with good prognostic value depending on the amount and speed of SBP recovery.

Because of the complex nature of aging processes, present reductionistic methods are not adequate for defining good health or healthy aging. Due to its

capacity to characterize complex dynamics within and between physiological systems, the emerging field of complex systems biology and its array of quantitative tools, such as the aforementioned critical slowing down, show great promise for improving our understanding of aging, monitoring senescence, and providing biomarkers for evaluating novel interventions that treat age-related disease and promote healthy aging.(72-74) Future research should focus on the determination of early signs of imminent transition states, so called frailty states, of the complex system of organ function interactions. Hereby, not only prognosis, but also prevention of complications by early detection of frailty states may become possible.

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Chapter 8

Summary in Dutch *Samenvatting in het Nederlands*

Dankwoord

List of publications

Curriculum vitae

Samenvatting

Dit proefschrift gaat over bloeddruk regulatie en cerebrale autoregulatie bij enerzijds oudere patiënten die een val-en-syncope-polikliniek bezochten en anderzijds patiënten met een Alzheimer dementie (AD). Dit proefschrift behandelt de volgende vragen: 1) delen orthostatische hypotensie (OH), postprandiale hypotensie (PPH) en carotis sinus overgevoeligheid (CSH) een gemeenschappelijke pathofysiologie en voorspellen ze mortaliteit? 2) Voorspellen de bloeddruk daling direct na opstaan, en de mate van bloeddruk herstel, mortaliteit? 3) Is AD van invloed op de baroreflex gevoeligheid (BRS) en beïnvloedt cholinesteraseremmer gebruik deze BRS? 4) En ten slotte, tast AD de dynamische cerebrale autoregulatie aan?

OH, PPH en CSH zijn aandoeningen van de bloeddruk regulatie met een hoge prevalentie bij ouderen. De exacte pathofysiologie van deze hypotensieve syndromen is niet duidelijk en zelden samen bestudeerd. Het cardiovasculaire autonome systeem speelt een belangrijke rol in de korte termijn regulatie van de bloeddruk. In **hoofdstuk 2a** vergeleken we 14 verschillende niet-invasieve autonome indices van de hartslag variabiliteit (HRV), bloeddruk variabiliteit (BPV) en BRS in een cohort van 203 patiënten die onze val-en-syncope-polikliniek bezochten. We vonden geen verschillen in deze indices tussen geriatrische patiënten met een van deze hypotensieve syndromen in vergelijking met geriatrische patiënten zonder een van deze hypotensieve syndromen. Er was ook geen verschil in deze indices tussen patiënten met en zonder valpartijen, duizeligheid of syncope. Deze resultaten pleiten tegen autonome dysfunctie als enige of dominante factor in de etiologie en pathofysiologie van deze hypotensieve syndromen. Het onderstreept ook de noodzaak van een multifactoriële aanpak in diagnostische onderzoeken van ouderen met vallen en/of syncope.

In **hoofdstuk 3a** onderzochten we of er indirect bewijs is voor een gedeelde pathofysiologie in OH, PPH en CSH. Hiertoe hebben we gekeken naar de aanwezigheid van deze drie syndromen in een cohort van 313 patiënten die onze val-en-syncope-polikliniek bezochten (dit cohort omvat ook de 203 patiënten van hoofdstuk 2). We bestudeerden het co-optreden van OH, PPH en CSH in dezelfde patiënt en bepaalden of dat vaker optrad dan het toeval. Hoewel OH, PPH en CSH een hoge prevalentie hadden van respectievelijk 54%, 58% en 53%, en dus vaak samen voorkwamen in dezelfde patiënt, was er geen sprake van clustering van deze syndromen. Deze afwezigheid van clustering suggereert verschillende onderliggende pathofysiologische mechanismen voor deze drie verschillende hypotensieve syndromen. Naast clustering, onderzochten we ook

de impact van deze hypotensieve syndromen op mortaliteit. Gedurende een mediane follow-up van 23 maanden overleden 58 (19%) patiënten. OH, maar niet PPH of CSH voorspelde mortaliteit (hazard ratio: 1,97; 95% betrouwbaarheidsinterval: 1,11 - 3.47). Deze relatie was niet meer significant na correctie voor leeftijd, comorbiditeit en andere baseline kenmerken. Echter, OH met een diastolische bloeddruk daling van 20 mmHg of meer bleef, ook na correctie, een krachtige onafhankelijke voorspeller van mortaliteit (hazard ratio: 2,50; 95% betrouwbaarheidsinterval: 1.20 -5.22), en kan daarom prognostisch gebruikt worden als een gemakkelijk beschikbaar cardiovasculaire maat van een toegenomen sterfterisico.

Terwijl in het vorige hoofdstuk werd gekeken naar de invloed van de bloeddruk daling tussen 1 en 3 minuten na opstaan (OH) op mortaliteit, onderzochten we in **hoofdstuk 4** de associatie van sterfte met de bloeddruk daling en ook het herstel in de eerste minuut na opstaan. Dit werd gedaan in een cohort van 238 patiënten die onze val-en-syncope-polikliniek bezochten als onderdeel van het grotere cohort van 313 patiënten beschreven in hoofdstuk 3. Gedurende een mediane follow-up van 21 maanden overleden 36 (15%) patiënten. De systolische en diastolische bloeddruk daalden gemiddeld maximaal met 42 ± 25 mmHg en 23 ± 15 mmHg binnen de eerste 15 seconden na opstaan, hetgeen overeenkomt met 75 ± 15% en 71 ± 16% van de baseline systolische en diastolische bloeddruk. Noch de absolute, noch de relatieve bloeddruk daling direct na opstaan voorspelden mortaliteit. Echter, het percentage herstel van de bloeddruk 40 tot 60 seconden na opstaan is wel geassocieerd met oversterfte, zelfs na correctie voor leeftijd, comorbiditeit en andere baseline karakteristieken. Een systolisch bloeddruk herstel van minder dan 80% van de uitgangswaarde na 60 seconden was een krachtige onafhankelijke voorspeller voor mortaliteit (hazard ratio: 3,00; 95% betrouwbaarheidsinterval: 1,17 - 7,68).

AD is een veel voorkomende progressieve neurodegeneratieve aandoening die een zware last legt op de samenleving en individuele zorgverleners. Cardiovasculaire factoren worden algemeen aanvaard als risicofactoren voor AD, maar de precieze relatie tussen deze factoren en AD blijft onduidelijk. Het cholinerge systeem (waaronder de baroreflex) is een belangrijk onderdeel van de cardiovasculaire en autonome regulatie, en AD tast dit cholinerge systeem mogelijk aan. Daarom is in **hoofdstuk 5a** de baroreflex bestudeerd in 18 AD patiënten, in 11 patiënten met milde cognitieve stoornissen en in 19 leeftijd en geslacht gematchte gezonde controles. De baroreflex is verminderd in AD in vergelijking met patiënten met milde cognitieve stoornissen en de gezonde controles. Dit resultaat werd gereproduceerd in een onafhankelijke validatie steekproef van 16 AD patiënten, 18 patiënten met milde cognitieve stoornissen en 19 leeftijd en geslacht gematchte gezonde controles. De behandeling van 18 AD patiënten met een

acetylcholinesteraseremmer verhoogde de baroreflex gevoeligheid met 66%. Samengevat is de baroreflex verminderd in AD en neemt deze toe na behandeling met acetylcholinesterase remmers. De pathofysiologische en diagnostische betekenis van deze verminderde baroreflex in AD vergt nader onderzoek.

Tenslotte wordt in **hoofdstuk 6** de dynamische cerebrale autoregulatie en de hersenweefsel-oxygenatie in AD bestudeerd. Bij 21 patiënten met een milde tot matige AD en 20 leeftijd en geslacht gematchte controles, onderzochten we hoe oscillaties van de cerebrale bloeddoorstroming snelheid (CBFV) en hersenweefsel-oxygenatie (O_2Hb) gerelateerd zijn aan oscillaties in bloeddruk geïnduceerd door herhaalde zit-sta manoeuvres met een frequentie van 0,05 Hz en 0,1 Hz. In AD was de cerebrovasculaire weerstand 34% hoger in vergelijking met de leeftijd gematchte controles. Ondanks een hogere cerebrovasculaire weerstand was er geen verschil in de dynamische autoregulatie tussen patiënten met AD en gezonde controles. Echter, bij patiënten met AD was de overdracht van CBFV naar O_2Hb anders dan in de controle personen. De verhoogde cerebrovasculaire weerstand en de veranderde overdracht van de cerebrale bloedstroom naar de hersenweefsel-oxygenatie, zou kunnen wijzen op veranderde eigenschappen van de cerebrale microvasculatuur of een veranderd oxidatief metabolisme van het hersenweefsel in AD.

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Curriculum Vitae

Joep Lagro werd in Nijmegen geboren op 24 mei 1972. Na zijn VWO diploma gehaald te hebben aan de Nijmeegse Scholengemeenschap Groenenwoud (NSG), begon hij in 1990 met de opleiding werktuigbouwkunde aan de Technische Universiteit te Delft. In 1992 startte hij met de opleiding geneeskunde aan de Rijksuniversiteit te Leiden. Het afstudeeronderzoek voor werktuigbouwkunde (vakgroep Meet- en Regeltechniek, Mens-Machine Systemen) en de opleiding geneeskunde werd gecombineerd uitgevoerd op de afdeling Medische Fysica (prof. dr. ir. Jos Spaan) van het AMC te Amsterdam onder begeleiding van prof. dr. Jenny Dankelman en prof. dr. ir. Henk Stassen† In 1999 behaalde hij met cum laude zowel zijn doctoraal examen geneeskunde als zijn ingenieursexamen werktuigbouwkunde. Het artsexamen werd in 2001 met cum laude behaald om vervolgens als agnio interne geneeskunde te gaan werken in het Rijnland ziekenhuis te Leiderdorp (opleider dr. Frans Cluitmans). In 2003 startte hij met de opleiding interne geneeskunde in het LUMC te Leiden (opleiders prof. dr. Edo Meinders en later prof. dr. Hans Romijn) om in 2007 voor het aandachtsgebied ouderengeneeskunde (opleider prof. dr. Rudi Westendorp) te kiezen. Na afronden van de opleiding tot internist-ouderengeeneeskunde is hij sinds 2009 als staflid verbonden aan de afdeling klinische geriatrie van het UMC St. Radboud te Nijmegen (afdelingshoofd prof. dr. Marcel Olde Rikkert). In 2010 werd een aanvang gemaakt met dit promotietraject. Naast onderzoek, patiëntenzorg en opleiding houdt hij zich nadrukkelijk bezig met onderwijs. Per 2013 is hij benoemd tot junior Principal Lecturer. Joep is sinds 1997 samen met Valérie Héraud en zij hebben twee kinderen, Célia (2005) en Florian (2007).

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Joep Lagro was born in Nijmegen on May 24th 1972. After graduation in 1990 from secondary school at the "Nijmeegse Scholengemeenschap Groenenwoud (NSG)", he started with Mechanical Engineering at the Delft University of Technology. In 1992 he commenced with the study medicine at the Medical Faculty of the University of Leiden. His thesis for mechanical engineering (section Measurement and Control, Man Machine Systems) and medicine was combined and performed at the Department of Medical Physics (prof. dr. ir. Jos Spaan) of the Academic Medical Center Amsterdam under supervision of prof. dr. Jenny Dankelman en prof. dr. ir. Henk Stassen†. In 1999 he graduated cum laude for both his Master's of medicine and mechanical engineering. The medical degree was obtained cum laude in 2001 and hereafter he started working as a house officer not in training internal medicine at the Rijnland Hospital Leiderdorp (supervisor dr. Frans Cluitmans). In 2003 he started his

internal medicine fellowship training at Leiden University Medical Centre (supervisors prof. dr. Edo Meinders and later prof. dr. Hans Romijn) and he choose for the subspecialty old age medicine in 2007 (supervisor prof. dr. Rudi Westendorp). After he became board certified, he joined the staff of the department of Geriatric Medicine of the Radboud Nijmegen University Medical Centre (head prof. dr. Marcel Olde Rikkert). In 2010 he became involved in research and started this thesis. Beside research, patient care and training he is specially involved in medical teaching. As from 2013 he is appointed as junior Principal Lecturer. Joep is together with Valérie Héraud since 1997 and they have two children, Célia (2005) and Florian (2007).